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REGIONAL EFFECTS OF VARYING LEVELS OF FLOW DURING EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO) IN CONJUNCTION WITH ALVEOLAR NORMOXIA AND HYPOXIA IN NEWBORN PIGLETS.

BY

Winston K.Y. Chan, M.D.

A thesis submitted to the faculty of graduate studies and research in partial fulfillment of the requirements for the degree in **MASTER OF SCIENCE**

IN

EXPERIMENTAL SURGERY

DEPARTMENT OF SURGERY

EDMONTON, ALBERTA

FALL, 1992

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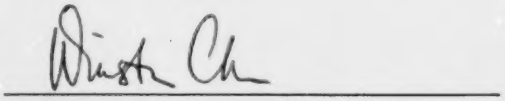

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ABSTRACT

Venoarterial extracorporeal membrane oxygenation (ECMO) is a form of life support than can substitute all or part of pulmonary or cardiac function. Support is provided to the patient with failing heart or lungs, with the hope that those organs will recover. A number of complications occur in the ECMO treated population and there is a concern that compromised myocardial function may be a complication of such therapy. We attempt to address issues of possible cardiac morbidity with this form of life support and to evaluate myocardial oxygen delivery and performance. Venoarterial ECMO was performed in 7 neonatal piglets (4-10 days of age) to determine the effect of increasing ECMO flow on myocardial, cerebral and systemic oxygen delivery, myocardial and systemic oxygen metabolism, blood flow, and vascular resistances. Measurements were taken before and after cannulation and at ECMO flows of 40, 80, and 120 mL/kg/min. At each flow level measurements were recorded while ventilating the lungs with oxygen (FiO_2=0.6), and during alveolar hypoxia induced by ventilating with nitrogen. The right carotid artery flow and oxygen delivery, left carotid flow and oxygen delivery, coronary artery flow and oxygen delivery, myocardial oxygen consumption and extraction, percentage coronary filling from left ventricle, cardiac index, systemic oxygen delivery, consumption, and extraction, pulmonary vascular resistance, and systemic vascular resistance were determined.

Right carotid artery ligation and cannulation increased left carotid artery flow and oxygen delivery ($p<0.05$) but decreased total carotid artery flow and oxygen delivery (a reportedly observed trend that did not however reach statistical significance). All flow rates of ECMO further decreased total carotid artery blood flow and oxygen delivery compared to baseline ($p<0.05$). Myocardial oxygen consumption was lowest while at an ECMO flow of 120 mL/kg/min with oxygen ventilation ($p<0.05$). Myocardial oxygen consumption increased with decreasing levels of bypass and was further increased by hypoxia. Indexed systemic vascular resistance significantly decreased from 1.15 mmHg/mL/min/kg at baseline to 0.74 at an ECMO flow of 120 mL/kg/min ($p<0.05$). Coronary blood flow and oxygen delivery were linearly related to myocardial oxygen consumption ($p=0.000$, $r=0.6559$; $p=0.000$, $r=0.7965$). Sixty-two percent of coronary blood flow was derived from the left ventricle at 40 mL/kg/min compared to 47% at 120 mL/kg/min (p=ns). The majority of coronary blood flow was derived from the left ventricle except during very high bypass flows (81% bypass) ($p<0.05$). Pulmonary vascular resistance was significantly lower on ECMO while ventilating with oxygen at all flow rates compared to ECMO during hypoxia ($p<0.05$). Pump venous oxygen content was similar to pulmonary artery oxygen content at all flow rates except 40 mL/kg/min during alveolar hypoxia ($p=0.000$, $r=0.9708$). Systemic oxygen delivery was greater than or equal to baseline values at all flow rates except 40 mL/kg/min during alveolar hypoxia ($p<0.05$). We conclude that in the neonatal piglet: 1) at all flow rates ECMO decreases total carotid artery blood flow and oxygen delivery; 2) full support ECMO provides maximal cardiac rest as determined by myocardial oxygen consumption and decreased measured afterload; 3) alveolar hypoxia increases pulmonary vascular resistance despite arterial normoxia or hyperoxia provided by ECMO; 4) monitoring using pump venous blood adequately reflects mixed venous blood; and 5) ECMO provides systemic oxygen delivery which is greater than or equal to baseline at all flow rates except 40 mL/kg/min during alveolar hypoxia.

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LIST OF ABBREVIATIONS

ARDS - adult respiratory distress syndrome

CBF - cerebral blood flow

ECMO - extracorporeal membrane oxygenation

HFOV - high-frequency oscillatory ventilation

PFC - persistence of fetal circulation

PPHN - persistent pulmonary hypertension of the newborn

VA - venoarterial

VV - venovenous

Chapter 1

INTRODUCTION

In recent years extracorporeal membrane oxygenation (ECMO) has increasingly been used to support neonates with otherwise lethal but reversible pulmonary disease[Toomasian et al., 1988]. Persistent pulmonary hypertension of the newborn (PPHN) is the major pathophysiologic mechanism of respiratory failure in the full-term newborn, regardless of the lung's underlying disease process[Lyrene and Phillips, 1984]. PPHN results in a condition previously referred to as persistence of fetal circulation (PFC). PFC is characterized by a patent ductus arteriosus and foramen ovale as well as very high pulmonary vascular resistance. This results in a right to left shunt which diverts blood away from the lungs and less than 10% of systemic blood flow passes through the pulmonary artery. This is adequate in utero as gas exchange occurs via the placenta and not the lungs. Outside the uterus, PFC with diversion of blood away from the lungs can be lethal. It is in this situation that ECMO can be lifesaving. ECMO theoretically works by arresting the cycle of increasing pulmonary hypertension (a cycle which results in PFC in the neonate) by minimizing the lung complications of high-pressure mechanical ventilation, and by allowing time for the pulmonary pathology to resolve and the lung to heal[Graves et al., 1988].

The Royal Alexandra Hospital in Edmonton initiated its' ECMO program in 1989. Until September of 1991, Edmonton's Royal Alexandra Hospital was the only Canadian center offering ECMO support. Since then ECMO programs in Montreal and Toronto have been initiated. Currently, neonatologists from the Division of Newborn Medicine in the Department of Pediatrics, and surgeons from the Department of General Surgery with

vascular and pediatric subspecialty training have provided ECMO for a total of 62 newborn infants (Appendix I).

ECMO is a relatively new procedure and there is little information available which examines the effects of ECMO on regional blood flow, oxygen delivery, oxygen consumption, or the source of myocardial oxygenation. Numerous studies of the physiology of extracorporeal circulation as used for cardiac surgery have been performed; whether those studies can be applied to ECMO is questionable. ECMO is different in a number of important ways including length of support, the degree of anticoagulation, the extrathoracic cannulation, and the need to provide support to extremely hypoxic and often hypotensive patients, to name a few. As well, during cardiopulmonary bypass in the operating room, no vessels are ligated, drainage of both the inferior and superior venae cavae is captured, and the perfusion cannula is positioned in the aortic arch or retrograde from the femoral artery. In addition, the myocardium is protected with intermittent doses of cold cardioplegic solutions injected into the aortic root and often hypothermia is utilized. In contrast, during ECMO, the internal jugular vein and carotid artery on the right side are permanently ligated distal to the cannulas. Only a portion of the venous return to the heart is captured with a venous cannula in the right atrium. The perfusion cannula is in the innominate artery, and no special protection can be applied to the heart or coronary circulation[Nowlen et al., 1989].

Even though ECMO has been shown to improve survival of neonates in respiratory failure, the procedure is not without risk. There are a number of complications that occur during ECMO. These include intracranial infarction or hemorrhage (14% on ultrasound and 3% on computer assisted tomography scan), major neurologic deficits, which includes cases of hemiplegia (2%) and hemiparesis seizures (16%), gastrointestinal hemorrhage (4%), bleeding from surgical site (14%), hemolysis (8%), renal failure requiring dialysis or

hemofiltration (10%), cardiac arrest necessitating cardiopulmonary resuscitation (3%), and hypertension (11%)(Toomasian et al., 1988). A confounding problem is that the population that is eligible for ECMO support is the same population already at high risk for developing these complications even without ECMO. Thus it is difficult to determine whether the complications occur secondary to ECMO or to their clinical state prior to ECMO. Many of the effects of ECMO support and the corresponding physiologic changes (which may contribute to the complications of ECMO) remain to be determined.

Chapter 2

BACKGROUND

PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

Respiratory failure is the leading cause of death in the neonatal period (Graves et al., 1988). PPHN is the major pathophysiologic mechanism of respiratory failure in the full-term newborn regardless of the underlying disease process (Lyrenne and Phillips, 1984). The clinical syndrome of PPHN or PFC, consists of intense pulmonary vasoconstriction, right-to-left shunting through the ductus arteriosus and/or foramen ovale, and severe hypoxemia without evidence of congenital heart disease (Weigel and Hageman, 1990). A number of conditions may result in PPHN, including meconium aspiration, hyaline membrane disease, neonatal sepsis with pneumonia, congenital diaphragmatic hernia, polycythemia, and hypoglycemia. The neonatal lung responds to hypoxia, hypercarbia, and acidosis with increased pulmonary vascular resistance (Fox and Duara, 1983). This increased resistance, which is the key to PPHN, impedes pulmonary blood flow and results in a right-to-left shunt via the foramen ovale and ductus arteriosus (Gersony, 1984). Thus blood passes from the right to the left side of the heart without circulating through the lungs resulting in life threatening hypoxemia, cyanosis and acidosis, and further pulmonary vasoconstriction. A vicious cycle is established where hypoxia causes vasoconstriction which causes further hypoxia and more vasoconstriction and so continues the cycle. Normally, immediately after birth, the infant takes a deep breath and the oxygen saturation of the pulmonary blood rises and the pulmonary vascular resistance decreases, resulting in disappearance of the fetal right-to-left shunt (Fox and Duara, 1983). Blood subsequently flows through the lungs and gas is exchanged.

PPHN may be classified as either primary or secondary as described by Levin[Levin, 1979]. Primary PPHN is defined as primary pulmonary vascular disease due to factors such as hypoxemia or acidemia, which alter the degree of constriction, or the muscularity or number of pulmonary vessels. Secondary PPHN includes conditions, such as meconium aspiration, that predispose infants to pulmonary vasoconstriction[Hageman et al, 1984].

PPHN may also be described in anatomical terms, based on pulmonary vascular morphology. The three types as described by Geggel and Reid are: 1) maladaption (where PPHN and PFC occur in structurally normal pulmonary vasculature); 2) excessive muscularization of the pulmonary vasculature; and 3) underdevelopment of the pulmonary vasculature[Geggel and Reid, 1984]. The first occurs in structurally normal lungs in response to a hypoxic, hypercarbic or acidotic stimulus. The second occurs in response to stimuli such as intrauterine exposure to indomethacin, aspirin, other prostaglandin synthetase inhibitors or anatomic obstruction of the pulmonary venous system, or chronic intrauterine stress or hypoxia. Murphy et al. also proposed that excessive muscularization may have resulted from prenatal insults, including: 1) increased sensitivity to intrauterine hypoxia or stress, causing chronic vasoconstriction and pulmonary vascular remodelling; 2) alteration of flow characteristics of the pulmonary vascular; and 3) failure of the mechanisms which normally regulate arterial muscularization and vascular tone[Murphy et al., 1981]. The third anatomical type, underdevelopment of the pulmonary vascular circulation, classically occurs in a neonate with congenital diaphragmatic hernia whereby the displaced abdominal contents retard lung development[Graves et al., 1988]. However, the pulmonary hypoplasia associated with congenital diaphragmatic hernia is not usually the cause of increased pulmonary vascular resistance as pointed out by Johnston et al. They deduce this by analyzing the "honeymoon period" after hernia repair, when ventilation is adequate for a period of time. Subsequently deterioration

sets in which is a vasospastic response of the muscularized pulmonary arteries to hypoxemia and acidosis(Johnston et al., 1988).

Mechanically assisted ventilation is the mainstay of therapy for PPHN; the most common form being hyperventilation and induced alkalosis(Graves et al, 1988). This is effective for treating the majority of infants with PPHN. Other commonly used interventions include muscle paralysing agents, inotropes, pulmonary vasodilators such as Tolazoline and ECMO(Weigel and Hageman, 1990). ECMO is required for the 2% to 5% of neonates that fail to respond to conventional therapy(Wung et al., 1985). The goal of either conventional or ECMO therapy is to interrupt the vicious cycle of hypoxia and acidosis and allow relaxation of the pulmonary vascular bed permitting pulmonary blood flow. Initially, ECMO was considered a salvage procedure and was reserved for those with an expected mortality of approximately 90%. As successful results accumulated, infants with less severe disease were entered into trials of ECMO. Presently in Edmonton only those infants fitting strict criteria[1] and having an expected mortality of 80-90% are eligible for this invasive therapy.

EXTRACORPOREAL MEMBRANE OXYGENATION

Venoarterial (VA) ECMO is a form of life support used to substitute all, or part of, pulmonary or cardiac function. In theory, the patient with failing heart or lungs is given support, to allow these organs to recover. Normal perfusion and gas exchange are maintained by ECMO usually without the use of inotropic drugs or application of high pressure ventilation to the heart and lungs, allowing the damaged organs to rest. ECMO can

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[1] Selection criteria include: an oxygen index greater than 40 on three occasions at least 30 minutes apart over a 2 hour period, during maximal ventilatory support with a mean airway pressure of at least 18 cm H_20, which predicts an 80% mortality (oxygen index = mean airway pressure *FiO_2*100/postductal PaO_2)(Finer, 1990).

be used for a number of days - up to weeks, to support the cardiopulmonary system of neonates, children, or adults.

There are two main types of cardiopulmonary support. VA bypass replaces the functions of the heart and lungs; VV bypass replaces the function of the lungs. It is the VA bypass which has become the standard mode of therapy for neonates. During VA bypass one concern regarding coronary oxygen delivery is the position of the arterial cannula. It is thought that the position of the cannula tip at the arch of the aorta distal to the coronary ostia may be responsible for an inadequate supply of oxygen to the heart. Thus, while the bypass is replacing the function of the heart by pumping blood, it may simultaneously be damaging the heart by reducing the delivery of well-oxygenated blood to the coronary arteries causing ischemia. VV bypass is not associated with this problem as the oxygenated blood is returned into the right heart proximal to the coronaries (venous side of the heart). In fact, there are fewer physiologic changes that occur with VV bypass, as the amounts of blood removed from the circulation and oxygenated, are equal to the amounts returned to the right heart. The major disadvantage of this system is that there is no replacement of the pumping action of the heart. In VV bypass, flow of blood through the body is entirely dependent upon the patient's heart.

Historically, as early as 1935, John Gibbon Jr., Clarence Dennis, and others began development of a mechanical device, that could replace the functions of the heart and lungs, to allow surgical procedures to be performed on the heart and great vessels. It was not until 1953 that their goal was realized when Dr. John Gibbon Jr. performed the first successful open-heart surgery using artificial oxygenation and perfusion support. Initially when extracorporeal circulation was used for more than a few hours the procedure became lethal as complications increased in proportion to the time that cardiopulmonary support was

provided. Experimental work by numerous investigators indicated that the direct exposure of blood to oxygen was responsible for the complications[Dobell et al., 1965]. Since then numerous important advances have been made which allow extracorporeal circulation to be used from hours to days to weeks. Advances include development of a silicone membrane which allows transfer of gases without direct blood gas contact, and low dose heparin titration which minimizes bleeding complications. Animal studies of extracorporeal circulation have provided the basis for early clinical trial of ECMO.

Hill reported the first successful use of ECMO in 1972 in a young man who had sustained multiple injuries from a motorcycle accident and whose injuries were complicated by Adult Respiratory Distress Syndrome (ARDS)[Hill et al., 1972]. Other adult cases of ARDS treated with ECMO were reported which led to a multicenter trial of ECMO for ARDS in 1975[Zapol et al., 1979]. The survival rate of both the control group and ECMO group was less than 10% and the trial was discontinued, with the investigators concluding that the major problem was not the technology of ECMO support but rather the underlying lung disease (extensive lung fibrosis was uniformly found at autopsy). Subsequently, clinical trials of adult ECMO for ARDS in the United States essentially stopped. There were, however, many criticisms which questioned the validity of the study, for example: 1) there were only nine centers involved in the trial and some of these centers had no previous experience with ECMO before the study began; 2) an epidemic of influenza pneumonia occurred in 1976 and patients affected by this made up the majority of subjects within the trial; 3) bleeding complications were excessive; and 4) the patients remained on high ventilator settings, even though the theory behind ECMO is to allow lung rest[Bartlett, 1990].

Gattinoni and Kolobow were not convinced of the results of the ECMO ARDS trial and subsequently they undertook a trial of venovenous (VV) ECMO in patients selected by

the same previous criteria. They emphasized avoidance of high airway pressure and high FiO_2; carbon dioxide removal via VV bypass using large membranes and low blood flows; low dose heparin and normal pulmonary blood flow to avoid microthrombosis or inhibition of lung healing[Gattinoni et al., 1986]. In 1986 they reported a 50% survival rate.

At present the selection criteria for children and adults to be provided with extracorporeal support, are based on the multicenter trial of ECMO and ARDS of 1975. The criteria used to select this patient population with a 90% risk of mortality are, transpulmonary shunting greater than 30% despite ventilatory or pharmacologic management and a static compliance consistently less than 30 mL/cm H_2O[Bartlett, 1991]. It is important to note that respiratory failure in children and adults differs from neonatal respiratory failure in that the lung diseases in the former group result in inflammation, fibrosis, infection, and necrosis. Pulmonary fibrosis is related to the degree of inflammation and the duration of lung exposure to high airway pressures and is the major cause of death.

The first neonatal ECMO survivor was treated by Bartlett in 1975[Bartlett et al., 1976], and since that time ECMO has been increasingly used. By 1986 there were 18 centers that had supported 715 neonates with ECMO. As of January 1992, 5863 neonates have been treated worldwide in 81 centers for respiratory failure with a survival rate of 82% (Appendix II). ECMO has proven to be successful in the treatment of neonatal respiratory failure and, as such, has become standard therapy for this syndrome in many centers. Two prospective randomized trials have shown that survival of full-term or near-term infants with respiratory failure is better with ECMO than with conventional ventilatory therapy[Bartlett et al., 1985; O'Rourke et al., 1989]. Other conditions, such as cardiac support, pediatric respiratory failure, and adult cardiac and respiratory failure, have been treated with ECMO a total of 905 times worldwide with lower survival rates (9%-65%) (Appendix II).

In neonates the application of ECMO is standardized and includes VA access via the right internal jugular vein and right common carotid artery; systemic anticoagulation using heparin titration based on whole blood activated clotting times; "lung rest" using low ventilator settings; and recognition that PPHN is the primary underlying pathophysiology(Bartlett, 1990).

The ECMO circuit draws blood from the right internal jugular cannula which has been inserted into the right atrium. The blood flows from the venous cannula by gravity into a bladder, or reservoir, and then is pumped with a roller pump past a membrane where gases are exchanged by a counter current mechanism. Oxygen is added and carbon dioxide removed. After being heated, the blood is returned to the patient's circulation via the right common carotid artery perfusion cannula, which is inserted so that its tip lies just within the aortic arch. Due to placement of the perfusion cannula in VA ECMO, oxygenated blood reenters the circulation distal to the coronary ostia. Various levels of ECMO support can be provided by increasing or decreasing the pump flow rate which regulates the amount of blood that passes by the membrane; thus support can be either partial or complete.

Chapter 3

NEUROLOGIC SEQUELAE OF ECMO

CLINICAL OBSERVATIONS

Despite encouraging results, ECMO is not without risk of injury to the brain. Standard VA ECMO requires systemic heparinization as well as ligation of the right common carotid artery and right internal jugular vein in order to access the heart. These factors, as well as the patient's physiologic response to decreased pulsatility of arterial flow, microemboli, and hypo- or hyperperfusion (causing ischemia or hemorrhage) relating to different flow rates of ECMO, are little understood and have all been suggested as potentially damaging to the central nervous system.

There is a high incidence of neuroimaging abnormalities in the ECMO treated population[Bowerman et al., 1985; Campbell et al., 1988; Luisiri et al., 1988; Schumacher et al., 1988; Taylor et al., 1987; Taylor et al., 1988; Taylor et al., 1989]. These intracranial complications, as detected by imaging techniques, occur between 10% and 47% of neonates treated. The severity of the intracranial abnormality appears to correlate with short-term developmental outcomes[Taylor et al., 1989].

While there is a high incidence of neuroimaging abnormalities, the incidence of major neurologic deficit after treatment with ECMO is generally around 10% to 25%[Schumacher et al., 1988]. This includes cases of left sided hemiparesis and hemiplegia[Krummel et al., 1984; Towne et al., 1985; Andrews et al., 1986]. In a recent study of neurological outcomes of neonates treated with ECMO at the Royal Alexandra Hospital, Robertson et al. report a 6% incidence of neurologic disability, a 12% incidence of neurodevelopmental dysfunction, a 9% incidence of cognitive delay, and a 15% incidence of motor delay[Robertson et al., in press]. In 1988 Bartlett reported

physiologic complications during ECMO in 715 patients as: a 14% incidence of intracranial hemorrhage detected by ultrasound; a 3% incidence of intracranial hemorrhage as detected by CT scan, severe neurologic impairment in 3%, seizures in 20%, and other neurologic abnormalities in 4%(Toomasian et al., 1988). Other experienced ECMO centers report that the majority of their patients are normal at 1 year(Adolph et al., 1990).

Although heparinization and ligation of the common carotid artery and internal jugular vein are direct risk factors, ECMO flow rates and regional flow changes could also result in hypo- or hyperperfusion of the brain with resultant ischemic or hemorrhagic injury. Reduced oxygen delivery which can exist in the presence of hyperperfusion (oxygen delivery is dependent on flow rate as well as oxygen content) may also be responsible for ischemic injury. Therefore, determining the level of ECMO flow which has the least effect on perfusion and which maintains optimal cerebral oxygen delivery could result in a practical guide for therapy.

EXPERIMENTAL STUDIES - CEREBRAL CIRCULATION

A number of experimental studies have been performed in an attempt to understand how ECMO affects the cerebral circulation. The experiments are not directly comparable to each other as flow rates of ECMO differed, as did the investigated aspects of cerebral circulation. The results varied greatly with disparate findings suggesting increased, decreased, or no change to cerebral and carotid artery blood flow and oxygen delivery.

The following two studies suggest that cerebral blood flow (CBF) or cerebral oxygen delivery may be decreased during ECMO. Smith injected albumin labelled technetium 99m via the perfusion cannula during VA ECMO at a flow rate of 50 mL/kg/min in lambs and showed that there was a significant increase in relative blood flow from the perfusion cannula to the total brain, when compared to normal left ventricular blood distribution without

bypass[Smith et al., 1989]. Microscopic examination of the brain after 71 to 96 hours of ECMO support revealed areas with anoxic change. Smith proposed that a decrease in hematocrit from 36% to 25% may have reduced oxygen delivery to the brain, to a greater extent than the increase in relative blood flow from the perfusion cannula, resulting in anoxic changes. Nowlen injected technetium labelled albumin into rabbits via the arterial perfusion cannula and then via the left ventricle during bypass at 30 mL/kg/min to determine blood flow from both the circuit and from the left ventricle during ECMO. He then injected radioisotopes into the left ventricle of animals not on bypass to determine the normal distribution of blood ejected from the left ventricle. They found that the percentage of CBF originating from the ECMO cannula represented 65% of the CBF in the non ECMO supported animal. The percentage of CBF originating from the left ventricle during ECMO represented 61% of CBF in the non ECMO supported animal. Oxygen delivery was decreased as a result of a decrease in hematocrit from 39% to 30%[Nowlen et al., 1989]. It is important to note that the two studies mentioned use a single injection of particulate matter. This allows determination of the portions of blood flow derived from the circuit and the heart during ECMO, but it does not allow changes in total blood flow to the brain to be assessed.

While the above two studies suggest that ECMO decreases cerebral oxygen delivery, two other studies infer that total CBF is not affected by ECMO. Kinsella et al. concurrently injected radiolabelled microspheres via the left ventricle and the ECMO cannula during VA ECMO flows of 50 and 100 mL/kg/min and found that ECMO at either flow rate did not change the total blood flow to the brachiocephalic artery[Kinsella et al., 1992]. However, blood from the ECMO cannula was preferentially directed to the brachiocephalic artery. Short used radiolabelled microspheres and catheters placed within the superior sagittal sinus during ECMO at flows of 120 mL/kg/min in lambs to determine the cerebral effects of

ECMO[Short et al., 1990]. Neither CBF nor oxygen metabolism (delivery, consumption, or extraction) changed after 30 and 120 minutes of support[Short et al., 1990].

Contrasting the above studies that infer that either CBF is decreased or not affect by ECMO, is a study by van de Bor et al. Their group used doppler to examine the pericallosal artery of infants during ECMO at different flow rates and reported an increase in blood flow velocity at higher ECMO flows. Significant increases were particularly rated at 60 to 120 mL/kg/min[van de Bor, 1990]. There was a correlation between mean arterial pressure and flow velocity but not between Hct, $Pa0_2$, $PaC0_2$ and CBF. Hct was kept greater than 45% with minimal difference at various levels of bypass. Thus estimated oxygen delivery also increased at higher ECMO flow rates in association with increased CBF velocity.

Another study, which cannot be directly compared to the above studies, as it solely evaluated carotid artery blood flow, rather than total CBF, was performed by Stolar et al. He inserted an epidural intracranial pressure monitor and placed a flow probe around the left carotid artery in lambs supported with ECMO at 100 to 120 mL/kg/min[Stolar and Reyes, 1988]. Stolar found that vessel ligation for cannulation caused no significant changes in left carotid artery blood flow nor intracranial pressure. ECMO support caused no significant changes in left carotid artery blood flow but decreased intracranial pressure. There is, however, no reference to the change in total (bilateral) carotid artery blood flow nor Hgb which would allow a calculation of oxygen content and delivery. Their only comment was that volume and Hct were maintained as needed.

Perlman et al. evaluated regional CBF using positron emission tomography in 11 infants after discontinuation of ECMO and ligation of the carotid artery and showed symmetrical regional CBF with no impairment of CBF to the hemisphere distal to the ligated

carotid artery. They concluded that ligation of the common carotid artery did not affect CBF following ECMO in the infants studied[Perlman et al., abstract #49, 1991].

Chapter 4

FACTORS AFFECTING CEREBRAL BLOOD FLOW

There are a number of factors that normally regulate CBF including, cerebral tissue metabolism, autoregulation, and the sympathetic nervous system. CBF is highly related to cerebral tissue metabolism with the metabolic components $C0_2$, 0_2, and pH, having the greatest effect. An increase in concentration of carbon dioxide or hydrogen ions, or a decrease in concentration of oxygen, increases CBF. Autoregulation is the phenomenon whereby CBF is maintained despite changes in arterial blood pressure within a specific range. In adult humans CBF is maintained extremely well between mean blood pressures of 60 and 140 mmHg, however, if the pressure falls below 60 mmHg CBF is compromised, and if the pressure rises above 140 mmHg, the upper level of autoregulation, CBF rises rapidly resulting in brain edema and vascular hemorrhage. Normally autoregulation overrides sympathetic control, but in some instances sympathetic stimulation can constrict the cerebral arteries markedly(Guyton, 1991a).

Studies have been performed which demonstrate these physiologic mechanisms are in fact in effect during ECMO. Taylor showed that cerebral autoregulation is preserved in infants during non-pulsatile cardiopulmonary bypass at temperatures greater than 26°C(Taylor et al., abstract #S153, 1990) and Walker demonstrated that cerebrovascular response to changes in $C0_2$ is not altered during ECMO(Walker et al., abstract #1363, 1988).

In contrast, van de Bor et al. found that high bypass flows correlated with increased mean arterial pressure and high CBF, and that low bypass flows correlated with decreased

mean arterial pressure and low CBF[van de Bor et al., 1990]. In their study mean arterial pressure ranged from 52-65 mmHg. This would indicate a lack of autoregulation during ECMO.

Chapter 5

CARDIAC SEQUELAE OF ECMO

CLINICAL OBSERVATIONS

There have been numerous reports of ventricular dysfunction during ECMO. This dysfunction ranges from arrhythmias to myocardial stun. Stunned myocardium represents prolonged, post ischemic ventricular dysfunction as defined by Braunwald in 1982(Braunwald and Kloner, 1982). Bartlett's 1988 study of physiologic complications occurring during ECMO reported a 5% incidence of ventricular dysfunction requiring cardiopulmonary resuscitation, a 4% incidence of arrhythmias, and a 13% incidence of other cardiovascular complications. Numerous other authors report cardiac complications during ECMO as follows.

In 1991 Martin reported cardiac stun in 12/240 (5%) infants undergoing ECMO(Martin et al., 1991). Neither changes in preload, afterload, nor addition of inotropes improved cardiac function. Cardiac stun was defined as an arterial pulse pressure of 10 mmHg or less, with an arterial PO_2 of 20 or less different from membrane lung oxygen. Echocardiogram showed near total absence of systolic cardiac function.

Also in 1991, Rosenberg reported four newborns with cardiorespiratory failure who developed signs of cardiac dysfunction and electromechanical dissociation early in the ECMO course(Rosenberg and Cook, 1991). This manifested as poor perfusion, pale color, narrow pulse pressure, and tachycardia despite normovolemia. Electromechanical dissociation occurred within 1 to 2 hours characterized by the absence of pulse pressure, palpable pulse, cardiac sounds, and apical impulse while on 50% to 70% bypass.

In 1988 Cater reported a case of stunned myocardium on day two in an infant treated with ECMO[Cater et al., 1988]. Cardiac dysfunction manifested during attempts to decrease the bypass flow to less than 80% of predicted cardiac output, which caused the patient to become severely hypotensive and shocked. Echocardiogram revealed a noncontracting left ventricle.

In 1990 Dickson performed echocardiography and creatinine phosphokinase measurements on 16 neonates before, during, and after ECMO (flow rates were not specified). They discovered that infants who developed a stunned myocardium on echocardiogram did so shortly after initiation of bypass, and that these same infants also had elevations of the myocardial band fraction of creatinine phosphokinase[Dickson et al., 1990]. Stunned myocardium was defined as a left ventricular shortening fraction decrease greater than 25% with a subsequent return to normal. The occurrence of cardiac complications and myocardial stun during ECMO leads one to question whether ECMO is having an adverse effects upon the heart.

It has been postulated that the clinical state of hypoxia and hypocarbia prior to ECMO may be the cause of myocardial dysfunction[Martin et al., 1991]. Martin found that cardiac arrest, before initiation of ECMO, occurred more often in infants with cardiac stun (50%), than in infants without cardiac stun (5.4%). Karr, however, investigated cardiac performance in neonates with severe respiratory failure treated with conventional therapy versus ECMO, and found no significant differences in myocardial performance which could account for the clinical deterioration which then required ECMO[Karr et al., 1991].

The state of the neonate prior to ECMO may contribute to the phenomena of myocardial dysfunction observed during ECMO. However, ECMO itself may affect cardiac performance as is suggested by the following clinical investigations.

Martin investigated 19 infants with PPHN using echocardiography performed before, during, and after ECMO(Martin and Short, 1988). With initiation of ECMO he found increases in blood pressure and afterload, no changes in heart rate, and decreases in left ventricular shortening fraction, pulmonary and aortic blood flow velocities, and contractility; thus concluding that ECMO has significant effects on cardiac performance.

Walther performed doppler ultrasonic examinations in 10 infants with life-threatening respiratory failure before, during, and after treatment with ECMO(Walther et al., 1990). Right and left ventricular outputs were evaluated to determine changes in cardiac performance associated with ECMO. Both left and right ventricular output decreased, as did left ventricular contractility, proportional to the amount of bypass flow provided.

Contradicting these studies is a report by Kimball who investigated 26 neonates with PPHN treated with ECMO(Kimball et al., 1991). Observations were made before ECMO, during maximum bypass, and after ECMO. There were no significant changes in contractility or afterload during the period studied even though there were decreases in ejection phase indices (cardiac output and shortening fraction) and heart rate, and increases in preload. As can be seen there are various effects of ECMO on myocardial performance reported in the literature.

EXPERIMENTAL STUDIES

Experimental work has been performed in the lab to help understand changes that occur with ECMO that might effect myocardial performance. Most of these experiments are too invasive to have been performed on either sick or normal neonates. There is evidence accumulating that ECMO may have detrimental effects on the heart in healthy and unhealthy animals. The following studies support the hypothesis that ECMO may be depriving the heart of oxygenated blood except at very high levels of bypass.

In 1984 Eugene created a model of heart failure in dogs[Eugene et al., 1984]. These animals were subsequently supported with ECMO while measurements of cardiac function were obtained. Initiation of ECMO was associated with a decrease in contractility of the heart, as compared to the baseline, as well as compared to the period of heart failure.

In 1974 Szczepanski performed ECMO in dogs to examine cardiopulmonary function[Szczepanski and Ornsholt, 1976]. During the experiment the dogs were placed on bypass equivalent to 40% of their cardiac output and allowed to breath spontaneously. Apnea occurred in 5 dogs and this was accompanied by myocardial ischemia as demonstrated by EKG findings of arrhythmias, changes in T waves, and deepening of Q waves, in spite of inflow of oxygenated blood. This investigation led to studies examining distribution of flow from the ECMO circuit.

Smith et al.[Smith et al., 1989] used albumin labelled technetium 99m injected via the perfusion cannula during VA ECMO at flow rates of 50 mL/kg/min in lambs and then compared this to injection via the left ventricle when not on bypass. They found that the percentage of coronary blood flow originating from the ECMO cannula represented 39% of the coronary blood flow in the non ECMO supported animal. After 71 to 96 hours of ECMO support the animals were euthanized and histologic examination of the heart showed anoxic changes, without infarction or inflammatory reaction.

Nowlen et al.[Nowlen et al., 1989] injected technetium labelled albumin into the left ventricle of rabbits not on bypass to determine the normal distribution of blood ejected from the left ventricle. Radioisotopes were then injected via the perfusion cannula and the left ventricle during ECMO at a flow rate of 30 mL/kg/min to determine blood flow from the circuit and the heart during ECMO. Their group found that the percentage of coronary blood flow originating from the ECMO cannula represented 45% of coronary blood flow in the non

ECMO supported animal. When comparing the left ventricular blood flow to cannula blood flow during ECMO, they found that left ventricular blood flow contributes 77% more to coronary blood flow than does blood flow from the cannula.

Secker-Walker et al. used catheters to sample oxygen concentrations from the left anterior descending and pulmonary arteries, the left ventricle, and the oxygenator, during VA bypass at incremental increases in flow rate in sheep to determine the source of coronary arterial blood flow[Secker-Walker et al., 1976]. They found that the coronary arterial tree is perfused with blood from the left ventricle except during high bypass flows (85% of cardiac output) or when the aortic valve is incompetent. Fifty percent of coronary blood flow is derived from the oxygenator when the oxygenator replaces 98% of total systemic flow (this only occurred with ventricular fibrillation).

Dudell and coworkers used catheters placed in the right internal carotid and pulmonary arteries, the left ventricle, and the aortic root to sample blood gases during VA ECMO at flows of 50-350 mL/min in puppies to determine the contribution of ECMO blood to cerebral and coronary blood flow[Dudell et al., abstract #1253, 1991]. They found that cerebral oxygenation is well maintained and coronary oxygenation is poor during neonatal ECMO and dependent on intrinsic pulmonary function. The weights of the animals were not specified so that a comparison of the level of bypass cannot be made. They did not comment on the actual proportions of flow from the left ventricle or ECMO cannula at these flow rates.

In 1988 Bavaria measured systolic stress integral, a primary determinant of myocardial oxygen consumption, during VA ECMO at flows of 20-100 mL/kg/min in sheep[Bavaria et al., 1988]. They found that in a dilated, poorly contracting heart, increases in ECMO flow increased left ventricular wall stress and, unexpectedly also increased myocardial contractility.

The preceding studies support the premise that ECMO may be depriving the heart of oxygenated blood except at very high levels of bypass. Thus the coronary circulation is dependent on either native lung function, if the lungs are ventilated, or deoxygenated mixed venous blood, if the lungs are not ventilated.

Regarding systemic oxygen metabolism, oxygen delivery (DO_2) is not directly matched to oxygen consumption (VO_2). Usually there is an excess supply of oxygen delivered to the tissues. A decrease in the rate of delivery is required before consumption is affected. In the systemic circulation a ratio of delivery to consumption (DO_2:VO_2) is normally 5:1 and theoretically, not until the ratio is less than 1:1 would VO_2 be affected. Practically, VO_2 is limited when the ratio is less than 2:1 in the systemic circulation[Bartlett, 1990]. Clinically, the mixed venous oxygen saturation reflects DO_2:VO_2 and thus sufficiency of DO_2 can be determined. Cornish found that ECMO flows of 50 mL/kg/min in newborn healthy baboons could provide adequate systemic DO_2 for short periods, but over longer periods flows greater than 100 mL/kg/min are probably necessary[Cornish et al., 1989].

There is minimal information regarding myocardial oxygen utilization during ECMO and DO_2:VO_2 ratios. As there may be a problem with DO_2 to the myocardium as is suggested in the preceding studies, an answer to the following question is required: At what level of myocardial DO_2 is myocardial VO_2 affected? The effects of ECMO on myocardial oxygen delivery, consumption, and extraction in the face of alveolar normoxia and hypoxia have not been studied. In addition as myocardial oxygen consumption is a reflection of cardiac work, the myocardial oxygen consumption is probably the best indicator of myocardial stress.

Chapter 6

FACTORS AFFECTING CORONARY BLOOD FLOW AND MYOCARDIAL OXYGEN METABOLISM

Blood flow through the coronary arteries is regulated predominantly by local needs of the cardiac musculature[Guyton, 1991b]. Although many mediators of metabolic activity of the heart are proposed to cause vasodilation, such as adenosine, adenosine phosphate compounds, potassium ions, hydrogen ions, carbon dioxide, and bradykinin, myocardial oxygen consumption is the major regulator of myocardial blood flow.

The second determinant of coronary blood flow is the autonomic nervous system. The autonomic nervous system affects coronary blood flow by direct and indirect means. Direct effects are via acetylcholine from the vagus nerve or norepinephrine from the sympathetic nerves which act on the coronary vessels causing diameter changes. Indirect effects are via increasing or decreasing activity of the heart which subsequently changes local metabolism thus affecting flow. The indirect effects play a far greater role in controlling coronary blood flow normally[Guyton, 1991b].

Myocardial oxygen consumption is an excellent measure of the chemical energy liberated while the heart performs its work; it is proportional to the tension multiplied by the duration of time the contraction persists[Guyton, 1991a]. Myocardial oxygen consumption, which reflects mechanical work, is determined by six factors[Sonnenblick and Skelton, 1971]. The three major factors are intramyocardial tension or stress/afterload (reflected by systemic vascular resistance), contractile state, and heart rate. Minor factors include external work (cardiac output), activation energy, and basal metabolism. During left heart bypass investigators have

found that myocardial oxygen consumption is related to the volume and pressure conditions of the left heart (e.g. left ventricular peak pressure[Jacobs and Hinglais, 1967] or left atrial pressure and left ventricular filling[Dennis et al., 1962].

At an intracellular level only a minute amount of oxygen is required for normal chemical reactions to take place. With cellular oxygen levels of greater than 1 to 3 mmHg, availability of oxygen is no longer a limiting factor. The limiting factor then becomes adenosine diphosphate. Thus under normal conditions the rate of oxygen utilization by the cells is controlled by the rate of energy expenditure within the cells. And only during very hypoxic states does oxygen availability become a limiting factor of myocardial oxygen utilization[Guyton, 1991c].

Chapter 7

LUNG MAINTENANCE DURING ECMO

Normally during ECMO the lung is "rested" with low inspiratory and expiratory pressures, low rates of ventilation, and low FiO_2. Theoretically no ventilation is required during full bypass. Recently investigators have advocated ventilating the lung while on ECMO for a multitude of reasons, which include decreased pulmonary vascular resistance, back up for mechanical failure of ECMO, and decreased atelectasis on chest x-ray. Examples within the literature follow.

Galantowicz et al. advocates ventilating the lung with oxygen during ECMO. In their experiment alveolar hypoxia increased pulmonary vasoconstriction to a greater extent than did arterial hypoxemia[Galantowicz et al., 1991]. Alveolar hypoxia significantly increased pulmonary vascular resistance despite arterial hyperoxia. Alveolar and arterial oxygen tension are independent, additive effectors of pulmonary vascular resistance. Thus reversal of increased pulmonary vasoconstriction, which is the key to PPHN, may be more sensitive to alveolar oxygen tension than increased arterial oxygen. Increased arterial oxygenation occurs during ECMO.

Cornish recommends the use of high-frequency oscillatory ventilation (HFOV) in combination with ECMO for the following reasons: 1) HFOV maintains critical lung inflation in a minimally traumatic fashion during ECMO; 2) HFOV potentially shortens the duration of ECMO (this trend occurred in his trial of 8 neonates); and 3) HFOV provides a safer ventilatory backup if there is mechanical failure of ECMO[Cornish et al., 1987]. (Mechanical

complications occurred in 23% of ECMO runs reported to the National ECMO Registry in 1988[Toomasian et al., 1988]).

Kezler also advocates support of the pulmonary ventilation during ECMO with high PEEP for the following reasons: 1) major component failures of ECMO are poorly tolerated with 4/9 (44%) within his series requiring transient removal from ECMO due to technical complications suffered; 2) severe atelectasis may have adverse effects on surfactant production (11/40 patients showed worsening of chest x-ray compared to baseline, whereas only 1/18 supported with positive end expiratory pressure greater than 12 cm H_2O showed deterioration); 3) high PEEP ventilation appears to decrease the duration (66 hours compared to 94 hours) of ECMO required and thus decreases the potential for exposure to complications of ECMO[Keszler et al., 1989].

Chapter 8

EVALUATION OF ECMO USING MIXED VENOUS OXYGEN SATURATION

CLINICAL OBSERVATIONS

While an infant is supported with ECMO the adequacy of systemic oxygenation provided by the bypass is usually assessed by the mixed venous oxygen saturation. This value reflects the balance between VO_2 and DO_2. The normal DO_2:VO_2 ratio is 5:1 and as VO_2 increases or decreases in response to changes to metabolism, the DO_2 is readjusted by increasing or decreasing the cardiac output to maintain the ratio 5:1[Bartlett, 1990]. If DO_2 decreases but VO_2 remains the same the only mechanism to compensate for this change is increased extraction of oxygen from the blood. There is a critical point to which DO_2 may decrease and extraction of oxygen may correspondingly increase to maintain VO_2. At lower levels than this VO_2 becomes dependent on DO_2. The critical point is reflected by the DO_2:VO_2 ratio of 2:1 with mixed venous oxygen saturation reflecting the DO_2:VO_2 ratios directly[Bartlett, 1990]. Thus mixed venous oxygen saturation has been used as a measure of the adequacy of oxygenation.

The pulmonary artery is the best place to acquire a sample of mixed venous blood as at this location adequate mixing of the blood from the superior and inferior vena cava has taken place through the right ventricle. Because of the complications associated with insertion of a pulmonary artery catheter (pneumothorax, hemorrhage, arrhythmias, etc.), compounded with its placement in an infant who is systemically anticoagulated and in whom a large #12-14 Fr venous catheter will be placed in the right atrium, alternatives to measuring the mixed venous oxygen saturation via the pulmonary artery have been employed.

As ECMO is practised today the blood from the intake port of the ECMO circuit, which is the venous catheter in the right atrium, is used to represent mixed venous oxygen saturation. Simply stated, right atrial blood is assumed to represent pulmonary artery blood. There are, however, problems with this assumption in the normal situation which involve streaming of superior and inferior vena cava flow and lack of adequate mixing. One would suspect that in the abnormal situation, where the blood is being partitioned by bypass, there may be errors with this almost universal assumption.

EXPERIMENTAL STUDIES

Investigators have shown that the oxygen content of blood within the right atrium has great variability which has been attributed to changes in the physiologic state, as well as incomplete mixing within the chamber(Barratt-Boyes and Wood, 1957). Normally, blood from the inferior vena cava is more fully saturated with oxygen than is blood from the superior vena cava but during shock the reverse occurs. Blood sampled from either central vessel or from the incompletely mixed right atrium may not be completely representative of the mixed venous oxygen saturation(Marini and Wheeler, 1989). Barratt-Boyes found a small but significant difference in oxygen saturation between the right atrium and pulmonary artery(Barratt-Boyes and Wood, 1957). Reinhart as well as Tahvanainen found that although changes in central venous oxygen saturation paralleled the changes in mixed venous oxygen saturation, the absolute values were not similar(Reinhart et al., 1989; Tahvanainum et al., 1982). Thus the assumption that right atrial oxygen saturation reflects mixed venous oxygen saturation during ECMO remains to be adequately validated.

Chapter 9

SUMMARY

ECMO is a relatively new technique associated with a number of associated mechanical and physiological complications. There are clinical sequelae which occur during and after ECMO which have been substantiated in the literature. Several studies have tried to outline the physiologic changes that occur in normal animals on ECMO. The effects of ECMO flow and the corresponding physiologic changes may contribute to complications, and further, organ specific information is required if we are to completely understand and properly apply this form of life support.

PURPOSE

There are three goals to study. The first goal is to develop a neonatal model to determine the effects of ECMO at various levels of bypass, on carotid (cerebral), pulmonary, myocardial and systemic oxygen hemodynamics in an effort to determine the level of support associated with maximal benefit and the least detrimental effects on these systems. The second goal is to determine whether alveolar oxygenation during ECMO at various levels of bypass can decrease some of the adverse physiological changes associated with ECMO. The third goal is to determine if measured right atrial blood accurately reflects true mixed venous blood.

HYPOTHESES

1) Ligation of the right common carotid artery and internal jugular vein for cannulation and varying flow rates of ECMO would affect left and total carotid artery blood flow and anterior cerebral oxygen delivery.

2) Myocardial oxygen delivery would be decreased during lower flow rates of ECMO which may result in myocardial stress or ischemia.

3) Ventilating the lungs with oxygen during ECMO increases oxygen delivery to the myocardium and improves myocardial oxygen consumption.

4) Ventilating the lungs with oxygen during ECMO decreases the detrimental physiologic changes, such as increased pulmonary vascular resistance that occur.

5) Right atrial venous oxygen saturation represents pulmonary artery oxygen saturation during ECMO support.

To our knowledge our study is unique in that it: 1) examined multiple flow rates of ECMO in a neonatal model (the exception being van de Bor's study of infants); 2) examined the effects of ECMO at multiple flow rates during both ventilation with oxygen and alveolar hypoxia; 3) quantified carotid oxygen delivery rather than determine trends; and 4) most significantly, determined myocardial oxygen metabolism during ECMO.

SIGNIFICANCE

If we could determine the changes that occur in CBF and cerebral oxygen delivery at different ECMO flow rates with and without alveolar oxygen, then the level of bypass with or without alveolar oxygenation which maximizes organ oxygen delivery could be used clinically, thus decreasing hypo- or hyperperfusion injury to the brain.

Only specific rates of ECMO flow may be found to support the myocardium's oxygen requirements (i.e. the level at which oxygen delivery becomes the rate limiting factor of oxygen consumption or myocardial mechanical performance could be optimized). Thus the bypass levels which best supports the heart, and causes the least detrimental effects with or without alveolar oxygenation, could be determined.

"Resting" of the lung may require higher FiO_2 and/or PEEP to decrease the adverse physiological changes that occur with ECMO support on the cerebral, myocardial, pulmonary, and systemic circulation. Clinically this would be important in post-operative cardiac surgical patients in whom lung function is usually preserved and in some neonates with primary cardiac dysfunction.

The clinical assumption that right atrial venous oxygen saturation represents pulmonary oxygen saturation may not be valid. Thus a more representative indicator of the adequacy of oxygenation may be required.

Restated, our goal is to determine some of the physiologic changes that occur with various levels of ECMO flow in the face of alveolar normoxia and alveolar hypoxia. This would hopefully assist the clinician in selecting the level of ECMO support with the least detrimental effects, as well as assist the clinician in deciding whether alveolar oxygenation during ECMO is beneficial. The data from out experiment could provide practical guidelines for clinical ECMO therapy including the minimum levels of ECMO used, the maintenance of the lung during ECMO, and the monitoring system to evaluate the clinical effectiveness of ECMO.

Chapter 10

MATERIALS AND METHODS

ANIMAL MODEL

The dog was initially our experimental animal of choice, as regional ECMO specialists presently use dogs during ECMO training. Other centers investigating ECMO have used different animals to simulate a neonatal model of ECMO; for example, dogs, puppies, lambs, rabbits, and piglets. However, local canine experience, combined with logistical problems with using lambs in our center due to health risks (i.e. causative agent: Coxiella burnetti→ Q fever, Appendix VII Zoonoses-Experimental Animals to Man, p. 93; Canadian Council on Animal Care, Volume 1), and previous unsuccessful attempts at developing a piglet model of ECMO, made the canine model a reasonable choice.

However, the dog model proved to be inadequate. Dogs provided by the Health Sciences Laboratory Animal Services were acquired from random sources, usually municipal pounds and as such the "Dogs have completely unknown genotypes, behavioral experiences and disease exposure profiles. Their use should be limited to those studies in which a defined animal is not a requirement. Dogs from random sources have often been discarded by their owners and turned loose to fend for themselves; thus, nutritional and disease problems will be frequently encountered in these animals" (Canadian Council on Animal Care). Thus inconsistencies in age, weight, breeding, and previous health were the source of too many variables. These deficiencies in the dog model, as well as an abundant supply of piglets, led us to reattempt developing a neonatal ECMO model in the latter species, which was successful. The piglet is in many respects the experimental animal of choice for

studies of ECMO. The swine possesses an end-artery coronary anatomy similar to that of the human heart[Horseffer et al., 1986] and cardiovascular physiology also resembles that of man[Lee, 1986]. Redding et al. showed that "the pulmonary vascular bed of newborn piglets and human neonates is similar morphologically in the immediate neonatal period and that functional characteristics also reflect those of neonates"[Redding et al., 1986]. In the piglet, the hemi-azygos vein drains directly into the coronary sinus. This vein allows direct access to the venous drainage of the heart, with minimal manipulation, and as such was ideal for evaluation of myocardial oxygen metabolism.

The main difficulties experienced in our piglet model of ECMO involve venous and arterial cannulation of the neck vessels to access the heart. The vessels are more friable and of smaller diameter than the corresponding vessels found in the human neonate. Two differences in piglet anatomy as compared to human anatomy required that changes be made in the cannulation procedure. The newborn piglet has a very small internal jugular vein which does not allow insertion of a cannula of appropriate diameter. Therefore, access to the right atrium was via the external jugular vein. The right internal jugular vein was ligated to simulate an infant's condition. In the piglet the right subclavian artery, right common carotid artery, and left common carotid artery originate from the brachiocephalic artery, unlike an infant where only the first two vessels originate from the brachiocephalic artery. Therefore, in the piglet, a right brachial artery sample was taken to represent blood originating from the brachiocephalic artery which was assumed to supply the left common carotid artery. Seven neonatal piglets (4-10 days of age, weight 3.2-3.9 kg) were studied.

SURGICAL PROCEDURE

Each animal was weighed and then anesthetized with Halothane 5% for induction, and Halothane 2% for maintenance. After intravenous access was obtained, Halothane was

discontinued and anesthesia was maintained with sodium pentobarbital (20 mg/kg IV, for induction, then maintained at doses of 5 mg/kg IV). The heart rate, respiratory rate, and rectal temperature were monitored continuously.

The right femoral artery was catheterized with a 5 Fr umbilical artery catheter (Elecath, Eledro Catheter Corp., Rahway, NJ) to monitor blood pressure, arterial blood gases, and hemoglobin. Crystalloids and blood were infused via the right femoral vein (5 Fr umbilical artery catheter) to maintain a hemoglobin between 11-13 g. A tracheostomy was performed and the animal intubated with a 4 mm I.D. endotracheal tube (Portex, Argyle, NY). Pancuronium bromide (100 μg/kg) was administered every 60-90 minutes, and a pressure-cycled ventilator (Healthdyne 105, Marietta, GA) was adjusted to maintain an arterial PO_2 greater than 70 mmHg and an arterial PCO_2 of 35-45 mmHg.

The right and left common carotid artery, and right internal and external jugular vein were exposed. A 2 mm transonic flow probe (HT 207, Transonic Systems Inc., Ithaca, NY) was placed around each carotid artery to measure blood flow. The right brachial artery was catheterized to monitor arterial blood gases originating from the brachiocephalic artery (the source of left carotid artery blood in a piglet). A thoracotomy was performed in the left fourth intercostal space and extended across the sternum. The hemiazygos vein was isolated, and a 5 Fr umbilical artery catheter was passed via this ligated vein into the coronary sinus to monitor coronary sinus blood gases. The left anterior descending coronary artery was isolated just distal to the bifurcation, and a 1 mm transonic flow probe was placed around it to monitor coronary blood flow. The aortic root was then isolated and a #20 gauge angiocatheter (Insyte, Sandy, UT) was placed with its tip within 1 cm of the coronary ostia, to monitor coronary ostial blood gases. A pressure tracing (HP77835, Hewlett Packard, Waltham, MA) was monitored to confirm placement within the aortic root rather than the

ventricle. The pulmonary artery was isolated and a 6 mm transonic flow probe was placed around it to monitor right ventricular output. A #20 gauge angiocatheter was placed in the pulmonary artery to monitor pulmonary blood pressure and pulmonary artery blood gases. A 3.5 Fr umbilical artery catheter was then placed within the left atrium to monitor left atrial blood pressure and pulmonary venous blood gases.

Blood gases were analyzed with a blood gas machine (Instrumentation Laboratory 1306, Milano, Italy). Hemoglobin was determined with a Coulter counter (M430, Coulter, Hialeah, FL). Sodium, potassium, chloride, and bicarbonate were determined with a Nova 1 (Nova, Newton, MA). Glucose was monitored using chemstrips (Chemstrip bG, Laval, PQ). All oxygen contents were calculated.

EXPERIMENTAL PROCEDURE

After a period of stabilization (a minimum of 30 minutes from complete instrumentation) a 10 minute observation of baseline was recorded. Blood was drawn for hemoglobin and blood gases were determined from the femoral and brachial artery, the coronary ostia and sinus, the pulmonary artery, and the left atrium. Then the common carotids, left anterior descending, and pulmonary artery blood flows, the systemic, aortic, pulmonary, and left atrial blood pressures, and the heart rate were recorded continuously for 5 minutes with a Hewlett Packard 78342A monitor. Data was continuously acquired at a rate of 24 Hz with a 486/25 CPU (Dell Computer Corp., Austin, TX), using the science/engineering package ASYST. A data acquisition program was written for this project (Aston Hugh, Royal Alexandra Hospital Neonatal Intensive Care Unit Research Department) using the ASYST language (ASYST Software Technologies, Inc., Rochester, NY). For the last 5 minutes of each phase the continuously acquired information was averaged and reported values reflect these continuously acquired averages.

The second phase of the experiment was performed to determine the effects of cannulation. Two differences in piglet anatomy as compared to human anatomy, required that changes be made in the cannulation procedure. The internal jugular vein was not cannulated, as is done in the neonate, since it is too small in the newborn piglet. Access to the right atrium was achieved via the external jugular vein using a 12 Fr venous cannula (Elecath, Eledro Catheter Corp., Rahway, NJ). This was used to drain blood from the animal to the ECMO circuit and to monitor right atrial blood gases. The right internal jugular vein was ligated to simulate an infant's condition. The carotid artery was cannulated with a 8 Fr arterial cannula which was advanced to the level of the aortic arch. This was used to return oxygenated blood from the ECMO circuit to the proximal aorta. After stabilization and a 10 minute period of observation, hemoglobin, blood gases, blood flows and pressures, and heart rate were recorded to determine the changes that occurred with cannulation.

Activated clotting times (ACT) were measured using a Hemochron 400 (International Technadyne, Edison, NJ). ACTs were controlled after a bolus of heparin (150-300 U/kg) and by continuous measurements of the ACTs and by adjusting the heparin infusion rate by senior ECMO specialists (Royal Alexandra Hospital ECMO Program) to maintain an ACT between 200-230 s.

The third phase of the experiment was to determine the effect of ECMO at 40 mL/kg/min during ventilation with oxygen. After completing phase 2, the ECMO flow was increased at a rate of 10 mL/kg/min to 40 mL/kg/min. Once at this flow rate of ECMO, the animal was allowed to stabilize and a hemoglobin and femoral artery blood gas were drawn. Adjustments in ventilation and oxygenation and sweep gas flow rate were performed to maintain the desired parameters of PCO_2 and PO_2. A 10 minute period of stability was

required before proceeding. Following this, blood gases were drawn from the six sampling sites as well as from the venous cannula (right atrium) and the arterial cannula (post membrane). The blood flows, pressures, and heart rate were again recorded for a 5 minute period.

The fourth and fifth phases were to determine the effect of ECMO at 80 and 120 mL/kg/min during ventilation with oxygen.

The sixth, seventh, and eighth phases were to determine the effects of ECMO support at 120, 80, and 40 mL/kg/min in the face of alveolar hypoxia. The percent contribution to the coronary artery from the ECMO circuit and the contribution from the left ventricle can be determined as reported by Secker-Walker[Secker-Walker et al, 1976].

While at an ECMO flow rate of 120 mL/kg/min, the inspired gas was then switched to nitrogen and ventilated for 5 minutes. The ventilator was then shut off and the animal allowed to stabilize. This created the condition of alveolar hypoxia with no oxygen contribution from the lung. ECMO then became the sole source of oxygenated blood.

ECMO was then decreased to 80 and then to 40 mL/kg/min, and the above procedures were performed again.

At the end of the experiment the animal was euthanized. The placement of all catheters and cannulas was confirmed by gross dissection.

ECMO CIRCUIT

The ECMO circuit was primed with blood which had been collected in CPD-N (Citrate-Phosphate-Dextrose) collection bags 48-72 hours prior from donor pigs. The equipment necessary to provide ECMO included a bladder box and controller (SMS 3200, 3100, SciMed Life Systems, Minneapolis, MN), roller pump (S10KII, Sarns Inc., Ann Arbor, MI), membrane oxygenation (800-2A 0.8 m^2 SciMed, SciMed Life Systems, Minneapolis,

MN), heat exchanger (Omnitherm P-7-14, SciMed Life Systems, Minneapolis, MN), blood warming unit (SMS 2000, Seabrook, Cincinnati, OH), and a full clinical ECMO cart which included pressure gauges, oxygen blender, oxygen analyzer (IE Medical, San Diego, CA), venous oxygen tension monitor (Cardiomet 1000, Toronto, ON), and ECMO circuit with a priming volume of approximately 430 mL.

PHYSIOLOGIC MEASUREMENTS

Pulmonary, common carotid, and left anterior descending artery blood flows were measured with transonic flow probes. Their measurements were used to represent right ventricular output, left and right carotid artery blood flow, and relative coronary blood flow.

Femoral, brachial, and pulmonary artery, left atrial, coronary ostia and coronary sinus, and pre- and post-ECMO arterial blood gases, as well as systemic, aortic, pulmonary, left atrial blood pressures, and hemoglobin were determined during each experimental phase.

CALCULATED VALUES

Cardiac index was calculated by dividing pulmonary artery flow by weight. Oxygen content was calculated using oxygen content = (Hgb) (%sat) (1.36) + (.003) (PO_2). Carotid oxygen delivery was calculated by multiplying blood flow by brachial artery oxygen content. An index of coronary oxygen delivery was calculated by multiplying left anterior descending artery blood flow by coronary ostial oxygen content. A relative index of myocardial oxygen consumption was calculated as a product of left anterior descending artery blood flow and the difference between the coronary ostial and coronary sinus oxygen contents. Myocardial oxygen extraction was calculated as the difference between the coronary ostial and coronary sinus oxygen content divided by the coronary ostial oxygen content. The systemic oxygen delivery was calculated by multiplying the sum of the cardiac index and the ECMO flow by the femoral artery oxygen content. The systemic oxygen consumption was determined by the

multiplying the sum of the cardiac index and the ECMO flow by the difference between the femoral and pulmonary artery oxygen contents. The systemic oxygen extraction ratio was calculated by dividing the difference between femoral and pulmonary artery oxygen contents by the femoral artery oxygen content. Systemic vascular resistance was calculated by dividing mean systemic blood pressure by the sum of the cardiac index and ECMO flow. (Right atrial pressure was not monitored.) The pulmonary vascular resistance was calculated by dividing the difference between pulmonary artery pressure and left atrial pressure by the measured pulmonary flow. The percentage of the coronary artery blood flow originating from the left ventricle can be determined from the following equation as described by Secker-Walker. The volume of blood supplying the coronary arteries (Q_{Lv}) originating from the left ventricle is reported as a percentage of total coronary blood flow (Q_{CA}).

$$\frac{Q_{Lv}}{Q_{tc}} = \frac{(C_{ECMO}) - (C_{CA})}{C_{ECMO} - C_{Lv}}$$

where Q_{Lv} is the volume of blood supplying the coronary arteries from the left ventricle and Q_{tc} is the total coronary blood flow. C_{ECMO} is the oxygen content of blood from the ECMO arterial cannula, C_{CA} is the oxygen content of coronary arterial blood, and C_{Lv} is the oxygen content of blood leaving the left ventricle, that is, the left atrial oxygen content. The above formula is derived from the following formulas:

$$(Q_{tc})(C_{CA}) = (Q_{Lv})(C_{Lv}) + (Q_{ECMO})(C_{ECMO})$$

and

$$Q_{tc} = Q_{Lv} + Q_{ECMO}$$

where Q_{ECMO} is the volume of blood supplying the coronaries from the ECMO circuit.

Percentage bypass is determined by the formula reported by Secker-Walker:

$$\% \text{ Bypass} = \frac{\text{ECMO flow}}{(\text{ECMO flow} + \text{Left ventricular output})} * 100$$

STATISTICAL METHODS

All data were coded, entered into a computer, and edited. Change within treatment groups were compared by paired t-tests with intergroup comparisons made by t-tests for unpaired variables or analysis of variance followed by a multiple comparison test when applicable.

An averaging of baseline values were made and comparisons between the 40, 80, and 120 groups both with (N) and without were made by analysis of variance. If there was an overall significant difference by analysis of variance, the least squares difference multiple comparison procedure was applied. Pearson correlation tests were applied to five key variables to determine relationships that might exist with the primary variables. The level of significance for all tests was $p<0.05$ unless otherwise stated.

Chapter 11

RESULTS

CAROTID ARTERY FLOWS

Ligation of the right neck vessels for cannulation increased the left carotid artery blood flow ($p<0.05$) and oxygen delivery ($p<0.05$), but decreased total carotid artery blood flow and oxygen delivery (although this did not reach statistical significance) (Figure 1). All flow rates of ECMO when ventilating with oxygen provided similar total carotid blood flow and oxygen delivery but these were further decreased in comparison to baseline ($p<0.05$). ECMO at 120 mL/kg/min during the phase of alveolar hypoxia provided a similar carotid oxygen delivery ($p<0.05$) by increasing carotid blood flow (although the increased blood flow did not reach statistical significance). Lower flow rates of ECMO during alveolar hypoxia resulted in further decreases in oxygen delivery ($p<0.05$). Thus, ECMO at all flow rates, with and without ventilation of the lungs with oxygen, resulted in decreased total carotid blood flow and oxygen delivery as compared to baseline ($p<0.05$).

CARDIAC OXYGEN METABOLISM

Changes in coronary blood flow and oxygen delivery paralleled changes in myocardial oxygen consumption ($P = 0.000$, $R = 0.6559$; $P = 0.000$, $R = 0.7965$) (Figures 2 and 3). When ventilating the lungs with oxygen at ECMO flow rates of 40 and 80 mL/kg/min the coronary blood flow and oxygen delivery, and myocardial oxygen consumption were similar to baseline. However, at 120 mL/kg/min during ventilation with oxygen, these values decreased. The lowest myocardial oxygen consumption observed occurred at 120 mL/kg/min during ventilation with oxygen ($p<0.05$). Coronary blood flow and oxygen delivery, and

myocardial oxygen consumption increased during alveolar hypoxia and with decreasing flow rates of ECMO ($p<0.05$). During ventilation with oxygen, systemic vascular resistance decreased as ECMO flow rates increased (Figure 4). At an ECMO flow of 120 mL/kg/min, systemic vascular resistance decreased significantly by 35% compared to baseline ($p<0.05$).

Sixty-two percent of coronary blood was from the left ventricle at flow rates of 40 mL/kg/min, but as ECMO flow rates increased to 120 mL/kg/min, the contribution from the left ventricle decreased to 47% (difference did not reach statistical significance) (Figure 5). Using the same variables as Secker-Walker, percent coronary filling from ECMO and percent bypass, our data can be subjected to the formula $y = a + bx$, in which $a = 0$, $b = 0.618$, and the correlation coefficient for our data points to this function is 0.53 ($p<0.05$) (Figure 6). The majority of coronary blood flow was derived from the left ventricle except during high bypass flows (81% bypass).

These changes in myocardial oxygen consumption occurred in conjunction with increases in afterload, heart rate, and cardiac output (Figure 4 and 7). It is important to note that this contrasted with ECMO during ventilation with oxygen which was not associated with increased afterload.

PULMONARY VASCULAR EFFECTS

Pulmonary artery pressure increased at all ECMO flow rates during alveolar hypoxia when compared to ventilation with oxygen ($p<0.05$) (Figure 8). Pulmonary artery flow rates decreased as ECMO flow rates increased, both during ventilation with oxygen and with alveolar hypoxia. Pulmonary vascular resistance increased at all ECMO flow rates during alveolar hypoxia as compared to ventilation with oxygen ($p<0.05$) (Figure 9). Pulmonary vascular resistance increased significantly during alveolar hypoxia, despite arterial normoxia or hyperoxia provided by ECMO.

MIXED VENOUS OXYGEN SATURATION

The oxygen content of the blood from the right atrium approximated the oxygen content of the blood from the pulmonary artery at all flow rates of ECMO except at 40 mL/kg/min during alveolar hypoxia where the difference increased ($P = 0.000$, $R = 0.9708$) (Figure 10).

SYSTEMIC OXYGEN METABOLISM

Systemic oxygen delivery and consumption were greater than baseline at all ECMO flow rates except 40 mL/kg/min during alveolar hypoxia ($p<0.05$) (Figure 11 and 12).

Systemic oxygen extraction (Figure 13).

Chapter 12

DISCUSSION

ECMO has been utilized to support infants with life-threatening respiratory failure refractory to conventional forms of therapy. Despite the success rate of ECMO numerous complications occur during this support. A confounding problem is that infants who are eligible for ECMO support are already at high risk for these complications. Thus it is difficult to distinguish whether the complications occur secondary to ECMO or to the clinical state prior to ECMO. In order to isolate the effects of ECMO, our study was performed on normal animals.

Our data suggest that ligation of the right neck vessels for cannulation, as well as undetermined aspects of the ECMO procedure itself, may contribute to cerebral ischemic injury. Ligation of the right neck vessels to access the heart decreased total carotid artery blood flow and oxygen delivery compared to baseline (although this did not reach statistical significance), and ECMO at all flow rates during ventilation of the lungs with oxygen further decreased these same values. In contrast to the majority of investigators in the related literature who evaluated only one flow rate of ECMO and did not quantitate cerebral oxygen delivery, our experiment examined the effects that both ligation for cannulation and varying flow rates of ECMO had on bilateral carotid artery blood flow and oxygen delivery. However, we were unable to determine total cerebral circulation as the procedure required to measure the vertebral arteries' contribution to total CBF was considered technically inaccessible.

There are a number of comparable studies that examine carotid artery blood flow. A study by Stolar and Reyes[Stolar and Reyes, 1988] inserted an epidural intracranial pressure monitor and placed a flow probe around the left carotid artery in lambs supported with ECMO at 100-120 mL/kg/min and found that vessel ligation for cannulation caused no significant changes in left carotid artery blood flow nor intracranial pressure. ECMO support caused no significant changes in left carotid artery blood flow but decreased intracranial pressure. They did not, however, make reference to the change in total (bilateral) carotid artery blood flow, nor Hgb, which would allow a calculation of oxygen content and delivery. Their only comment was that volume and Hct were maintained as needed.

Two other studies involving human infants receiving ECMO indicate that ligation and cannulation of the right carotid artery increases left carotid artery blood flow which is maintained during ECMO[Ichord et al., abstract #1139, 1987; Walther et al., abstract #2147, 1988].

In our animal model, it is probable that the brain compensated for the decrease in total carotid blood artery blood flow and oxygen delivery by increasing vertebral artery blood flow and oxygen delivery or by increasing cerebral oxygen extraction. Thus, although our experiment found a decrease in total carotid artery blood flow and oxygen delivery we are unable to comment upon total CBF and oxygen delivery.

Our data suggest that ventilating the lungs with oxygen during ECMO may decrease the risk of injury to the cerebral circulation. ECMO at flow rates of 120 mL/kg/min during alveolar hypoxia produced an increase in carotid blood flow that maintained the same carotid oxygen delivery as that provided by ECMO during ventilation with oxygen. This increased blood flow may contribute to the risk of intracranial hemorrhage. However, the question of whether it is beneficial to ventilate the lungs with oxygen during ECMO in a neonate with diseased lungs was not addressed in our experiment. In this circumstance of extrinsic

parenchymal disease secondary to pneumonia, meconium aspiration, or hyaline membrane, to name a few, an increased FiO_2 may produce little, if any, increase in left ventricular pulmonary venous oxygen content. The above findings suggest that if ECMO support is to be provided to neonates with normal, or near normal lungs, for example, in infants post cardiac surgery or infants with primary cardiac injury, the risk of cerebral injury may be decreased by ventilation with oxygen.

There are a number of cardiac complications that may potentially occur during ECMO support. As stated earlier, what is not clear is whether it is the clinical state prior to ECMO, or whether it is VA ECMO itself, or a combination of the two, that is the cause of myocardial dysfunction.

Our study differs from earlier studies performed by Smith, Nowlen, Secker-Walker, Dudell, and Szczepanski. These investigators examined the portion of coronary blood originating from both the oxygenator and the left ventricle (a function of native lung function). During less than full bypass, oxygen delivery to the coronary circulation from the ECMO arterial cannula decreased compared to left ventricular output of controls and was dependent on native lung function which in turn determines left ventricular oxygen content. They proposed that ECMO may be depriving the heart of oxygenated blood except at very high levels of bypass and that this may contribute to myocardial ischemia. A limitation of the above studies is that changes in total coronary artery blood flow could not be determined. In contrast, we measured left anterior descending artery blood flow and interpreted it as an index of total coronary blood flow. Our experiment suggests that total coronary blood flow and oxygen delivery decrease only at the flow rate of 120 mL/kg/min during ventilation with oxygen as compared to baseline. Coronary blood flow and oxygen delivery did not decrease during ECMO at flow rates of 40 and 80 mL/kg/min during ventilation with oxygen. These

results during ventilation with oxygen at the lower flow rates, are consistent with those of Kinsella et al.[Kinsella et al., 1992]. They measured changes in total coronary blood flow during VA ECMO flows of 50 and 100 mL/kg/min using double injections of particulate indicators. They found that ECMO at either flow did not change the total blood flow to the heart.

We found that during alveolar hypoxia and decreases in ECMO flow rate , coronary blood flow, oxygen delivery, and extraction increased. To determine the origin of coronary blood we used the formula, as reported by Secker-Walker et al.[Secker-Walker et al., 1976], which partitions blood according to oxygen content. The oxygen content of blood from the ECMO cannula is fully saturated with oxygen, whereas blood from the left ventricle is desaturated (the lungs were not ventilated, resulting in desaturated pulmonary venous blood). We found that 62% of coronary blood was derived from the left ventricle at flow rates of 40 mL/kg/min, but as ECMO flow rates increased to 120 mL/kg/min, the contribution from the left ventricle decreased to 47% (although this difference did not reach statistical significance).

It is important to note that at each flow rate of ECMO which we examined, the percentage bypass, as defined by Secker-Walker, varied greatly and was largely dependent upon pulmonary artery blood flow. At a flow rate of 40 mL/kg/min the percent bypass ranged from 20% to 47% with a mean of 30.5%. At a flow of 80 mL/kg/min the percent bypass ranged from 20% to 83% with a mean of 48.6%. And at an ECMO flow rate of 120 mL/kg/min the percent bypass ranged from 21% to 58% with a mean of 46.3%. Using the same variables as Secker-Walker, percent coronary filling from ECMO and percent bypass, our data can be subjected to the formula $y = a + bx$, in which $a = 0$, $b = 0.618$, and the correlation coefficient for our data points to this function is 0.539 ($p<0.05$) (Figure 7). If we are to compare our data with Secker-Walker et al., the results are very similar if the three data points plotted at 100% bypass in their experiment are excluded. Ventricular fibrillation

did not occur in our experimental model as it did in theirs and thus we were unable to achieve 100% bypass. In our experiment the ECMO circuit did not provide greater than 50% of coronary perfusion until greater than 81% bypass was provided by ECMO flow. Secker-Walker et al. showed that virtually total bypass (98%) is required before coronary arteries are supplied with 50% of oxygenator blood. An observation within their experiment which we are unable to account for is how the oxygenator can contribute only 66.7% to coronary filling if the percent bypass is 100% (inferring that there should be no contribution from the left ventricle). Both our experiment and theirs, however, show that the percent bypass must be very high for the majority of coronary perfusion to originate from the ECMO circuit. It is also important to note that both our experiment and Secker-Walker et al.'s examined the contribution to coronary perfusion under conditions of alveolar hypoxia (this condition was required to differentiate saturated blood from the oxygenator versus desaturated blood from the left ventricle). As such our experiments are not directly comparable to the experiments of Smith, Nowlen, or Kinsella. These authors examined the partitioning of blood during ECMO when the lungs were ventilated with oxygen or when the animals were breathing spontaneously. Our experiment shows that coronary blood flow and oxygen delivery during ECMO, when ventilating the lungs with oxygen, is very different compared to blood flow and oxygen delivery during alveolar hypoxia. Understanding the partitioning of blood during ECMO is only the preliminary step to comprehending how ECMO affects coronary blood flow and oxygen metabolism.

VA ECMO can temporarily support neonates with a failing heart, the physiologic basis for management involves control of the oxygen demand/supply ratio to the myocardium. It has not yet been determined how ECMO affects this ratio or which ECMO flow rate best supports the heart, as indicated by myocardial oxygen consumption. To our knowledge, we

are the first investigators to develop a neonatal model of ECMO which evaluates myocardial oxygen consumption at different flow rates of ECMO. It is important to note, however, that we did not calculate total myocardial oxygen consumption, as total coronary blood flow could not be measured. Rather, we determined an index of myocardial oxygen consumption by measuring left anterior descending coronary artery blood flow, again based on the assumption that changes in left anterior descending artery blood flow reflected changes in total coronary blood flow. Our experimental data shows that the changes in coronary blood flow and oxygen delivery paralleled changes in myocardial oxygen consumption. This is consistent with Guyton[Guyton, 1991b], who proposed that blood flow through the coronary arteries is regulated predominantly by the local needs of the cardiac musculature.

Another significant finding of our experiment is that ECMO support at 120 mL/kg/min was not associated with increased systemic vascular resistance (a measure of afterload), contrary to observations made by other investigators[Martin and Short, 1988]. Systemic vascular resistance (indexed) decreased as ECMO flow rates increased during ventilation with oxygen. At an ECMO flow of 120 mL/kg/min systemic vascular resistance decreased significantly by 35% compared to baseline. Though there had been previous concern that ECMO increased afterload, our research demonstrated that this is not the case.

Pulmonary artery blood flow (indexed) decreased by 63% at 120 mL/kg/min during ventilation with oxygen compared to baseline prior to ECMO, demonstrating that ECMO at high flow rates decreases cardiac output (Figure 8).

We also found that full ECMO support at flow rates of 120 mL/kg/min during ventilation with oxygen, provided maximal cardiac rest as determined by myocardial oxygen consumption. Consistent with Sonnenblick, our experiment demonstrated that decreased myocardial oxygen consumption was dependent upon decreased systemic vascular resistance

and cardiac output. Our finding that full ECMO support rests the heart agrees with previous studies designed to determine the conditions under which left heart bypass (which differs from ECMO as discussed earlier) takes over the work of the heart. Pennock demonstrated that the relationship between the level of bypass and the degree to which the heart was rested was nonlinear. There was minimal reduction of myocardial consumption until the point at which 80% of the output was provided by bypass. The greatest reduction of myocardial consumption (50%) occurred at total bypass[Pennock et al., 1974]. Jacobs demonstrated that coronary blood flow and myocardial oxygen consumption were not reduced in dogs until near total bypass occurred. He concluded that the reduction indicates the moment at which the left heart bypass takes over the work load of the left ventricle[Jacobs and Hinglais, 1967]. Dennis and co-workers likewise showed that total left heart bypass could reduce myocardial consumption by 50% compared to controls[Dennis et al, 1962].

The above studies support the theory that the condition with the lowest myocardial oxygen consumption indicates when the heart is maximally rested and when the heart has the greatest reserve. Thus, infants with myocardial injury or stun, or infants post cardiac surgery would benefit from this higher level of support. Currently, when the mixed venous oxygen saturation is adequate, ECMO flow rates are usually decreased. Our study suggests that full support ECMO should be maintained for a greater length of time in those infants with possible myocardial injury even though mixed venous oxygen saturation may be normal. In addition, current practice and convention is that 120 mL/kg/min is "full support" while it is clear that normal cardiac output in the neonate is probably twice this value. Thus higher levels of support may be required for severe myocardial injury. Other investigators have confirmed that even though the mixed venous oxygen saturation is normal, individual vascular beds may still be inadequately supplied with oxygen; that is, normal global oxygen delivery

may be present despite inadequate local oxygen delivery[Enger and Holm, 1990]. A study by Dahn revealed that splanchnic venous oxygen saturation was decreased at the same time that mixed venous oxygen saturation was either normal or increased[Dahn et al., 1988]. The mixed venous oxygen saturation is a mixture of all the end capillary blood oxygen contents from perfused tissue. High flow, low-consuming organs (kidney) will have a greater effect on the mixed venous oxygen saturation than will low flow, high-consuming organs (heart)[Enger and Holm, 1990]. Thus, even though right atrial or mixed venous oxygen saturation is adequate, it does not follow that coronary sinus oxygen saturation is adequate.

In our experiment myocardial oxygen consumption increased with alveolar hypoxia and further increased with decreasing levels of bypass. To explain why this occurred, we again examined the six factors which determine myocardial oxygen consumption as defined by Sonnenblick's findings[Sonnenblick and Skelton, 1971]. We found myocardial oxygen consumption to be dependent upon systemic vascular resistance, heart rate and cardiac output, consistent with Sonnenblick. We were unable to determine the remaining factors within our model: contractile state; activation energy; and basal metabolism. Fisher et al. reported that during hypoxia 80% of the increase in myocardial oxygen consumption is due to an adrenergic response induced by hypoxia[Fisher, 1989]. This may account for the increases in systemic vascular resistance, heart rate, and cardiac output that we observed in our experiment.

During ECMO the lung is normally "rested" with low inspiratory and expiratory pressures, low rates of ventilation, and low FiO_2. Theoretically no ventilation is required during full bypass. Investigators have advocated ventilating the lungs with oxygen (by increasing PEEP or using HFOV) while on ECMO for a number of reasons, including: 1) alveolar hypoxia significantly increases pulmonary vascular resistance despite arterial hyperoxia; 2) HFOV maintains critical lung inflation in a minimally traumatic fashion during

ECMO (severe atelectasis may have adverse effects on surfactant production); 3) HFOV potentially shortens the duration of ECMO (thus decreases the potential for exposure to complications of ECMO); and 4) HFOV provides a safer ventilatory backup if there is mechanical failure of ECMO.

When determining the physiological changes that occur with ECMO at varying flow rates, we specifically compared the changes that occurred during ventilation of the lungs with oxygen to those that occurred during alveolar hypoxia. Our results are consistent with those of Galantowicz. Galantowicz demonstrated that alveolar hypoxia is a more potent stimulant of pulmonary vasoconstriction than is arterial hypoxemia[Galantowicz et al., 1991]. He showed that alveolar hypoxia significantly increased pulmonary vascular resistance despite arterial hyperoxia and suggests that alveolar and arterial oxygen tension are independent, additive effectors of pulmonary vascular resistance. He also suggests that recovery from acute hypoxic pulmonary vasoconstriction, which is central to PPHN, may be more responsive to alveolar oxygen tension than increased arterial oxygen.

In our experiment pulmonary vascular resistance was lower at all flow rates of ECMO during ventilation of the lungs with oxygen as compared to ECMO during alveolar hypoxia. Thus, ventilating the lungs with oxygen may aid in reducing pulmonary vascular resistance which is the key to PPHN. It is of note that the decrease in pulmonary vascular resistance that occurred with ventilating the lungs with oxygen occurred in normal lungs. Whether a significant decrease in pulmonary vascular resistance would occur with oxygenation of diseased lungs is not addressed in our experiment.

During ECMO the blood is taken from the venous cannula located in the right atrium and is assumed to represent mixed venous oxygen saturation. There are problems with this assumption even within the normal situation, and consequently, we felt it was important to

test the validity of assuming that right atrial oxygen saturation reflects mixed venous oxygen saturation during ECMO.

Our data demonstrate that sampling of right atrial blood adequately reflects mixed venous oxygen saturation. We found that the right atrial oxygen content was very similar to the pulmonary artery oxygen content during all phases of the experiment except at flow rates of 40 mL/kg/min during alveolar hypoxia. At this flow rate during alveolar hypoxia we observed that pulmonary artery oxygen content was less than right atrial oxygen content. A possible explanation for this discrepancy is that approximately 15-25% of the heart's venous drainage flows directly into the right ventricle (the coronary sinus drains into the right atrium collecting approximately 75-85% of the heart's venous return). It is at this flow rate that myocardial oxygen consumption and extraction are maximal and the blood returning to the right heart is maximally desaturated; thus, the desaturated venous drainage directly entering the right heart could explain the difference. We conclude that right atrial blood adequately reflects pulmonary artery blood during ECMO.

We found that systemic oxygen delivery was greater than or equal to baseline at all flow rates except 40 mL/kg/min during alveolar hypoxia. This suggests that in a healthy animal model ECMO provides adequate systemic oxygen delivery at all flow rates excluding the above. To infer that these flow rates would supply adequate amounts of oxygen in the diseased animal or in the clinical situation would be inappropriate as adequacy of systemic oxygen delivery depends entirely upon systemic oxygen requirements. We found that as systemic oxygen delivery increased, so did systemic oxygen consumption. A possible explanation for this is provided by Ronco et al.[Ronco et al., 1991]. This group of investigators found that when oxygen consumption is directly measured it is independent of increases in oxygen delivery. However, if oxygen consumption is calculated from variables shared with

the calculation of oxygen delivery a dependent relationship is created. Thus questionable methodology applied in determining systemic oxygen consumption may be the source of the apparent increase in systemic oxygen consumption.

Our experimental model may not strictly reflect the clinical situation for a number of reasons. Clinically, during ECMO, infants are not anesthetized and do not undergo the invasive procedures of instrumentation and thoracotomy, procedures which in our model were necessary and required that the animal's chest remains open. As well, the brachiocephalic anatomy differs and, most importantly, the animal's lungs were normal in contrast to the clinical situation. Also, our experiment took place over a number of hours, and was not a chronic study, which would have more closely simulated the clinical situation. Type specific blood and pig albumin was not available to prime the ECMO circuit; carotid artery blood flow was examined rather than total CBF; and an index of coronary blood flow was measured in place of total coronary blood flow. Otherwise, all aspects of ECMO were delivered similar to the clinical situation.

Chapter 13

CONCLUSION

The neonatal piglet is a reasonable model for examining physiologic changes that occur with ECMO. Ligation for cannulation decreases total carotid blood flow and oxygen delivery (although this reportedly observed trend did not reach statistical significance). All levels of ECMO support were associated with further decreases in total carotid artery blood flow and oxygen delivery as compared to baseline. Full ECMO support decreases measured afterload and provides maximal cardiac rest as determined by myocardial oxygen consumption. The majority of coronary blood flow was derived from the left ventricle except during very high bypass flows (81% bypass). Despite full ECMO support and arterial normoxia, alveolar hypoxia increased pulmonary vascular resistance. Pump venous oxygen is an adequate indicator of mixed venous oxygen. Systemic oxygen delivery was greater than, or equal to, baseline at all flow rates except 40 mL/kg/min during alveolar hypoxia. These findings contribute to a to better understanding of the effects of ECMO at various levels of support and the physiologic changes which may be associated with the complications of ECMO.

From this study we recommend the following: 1) further more invasive studies are needed to evaluate total CBF and cerebral oxygen metabolism; 2) if ECMO support is to be provided to neonates with normal, or near normal lungs, such as in infants post cardiac surgery, the risk of intracranial hemorrhage due to increased CBF may be decreased by ventilating the lungs with oxygen; 3) full ECMO support, combined with ventilation with oxygen, can be provided to neonates with potentially injured myocardia for maximal cardiac

rest irrespective of mixed venous oxygen saturation; 4) ventilation with oxygen during ECMO in patients with diseased lungs requires further investigation to determine if there are any beneficial decreases in pulmonary vascular resistance; and 5) right atrial blood may be used to accurately represent mixed venous blood to determine the adequacy of systemic oxygenation.

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APPENDIX I

ECMO REGISTRY REPORT
(Extracoporeal Life Support Organization)

Royal Alexandra Hospital
EDMONTON, CANADA

Group	Total	# Survived	# Survived
Neonatal respiratory	43	36	84
Pediatric respiratory	2	2	100

NEONATAL CASES BY YEAR

Year on ECMO	Total	# Survived	% Survived
1989	14	13	93
1990	17	13	76
1991	12	10	83

NEONATAL CASES BY DIAGNOSIS

Primary Diagnosis	Total	# Survived	% Survived
MAS	16	16	100
RDS/HMD	2	1	50
CDH	11	6	55
Pneumonia/Sepsis	8	7	88
PPHN/PFC	3	3	100
Others	3	3	100

PEDIATRIC CASES BY YEAR

Year on ECMO	Total	# Survived	% Survived
1990	1	1	100
1991	1	1	100

PEDIATRIC CASES BY DIAGNOSIS

Primary Diagnosis	# Reported	# Survived	% Survived
Viral Pneumonia	2	2	100

APPENDIX II

ECMO REGISTRY REPORT
(Extracorporeal Life Support Organization)

Reported in part by a grant from the William Randolph Hearst Foundation, Inc.
January 1992

INTERNATIONAL SUMMARY

Group	Total Reported	Number of Survivors	Percent Survived	Number of Centers
Neonatal Respiratory	5863	4831	82%	81
Pediatric Respiratory	309	147	48%	55
Cardiac Support	545	250	46%	65
Adults (Resp./Card.)	51	19	37%	9
Total cases to date	6768			

ECMO CASES REPORTED BY REGISTRATION FORM ONLY

	Neonatal	Pediatric	Cardiac	Adult	Total
Number of cases =	215	35	35	4	289

NEONATAL CASES BY YEAR

Year	Total	Surv.	% Surv.
1973-79	35	18	51
1980	13	11	85
1981	16	9	56
1982	15	8	53
1983	16	14	87
1984	80	55	69
1985	207	168	81
1986	425	353	83
1987	649	562	87
1988	1006	847	84
1989	1103	912	83
1990	1309	1065	81
1991	989	809	82

NEONATAL CASES BY DIAGNOSIS

Diagnosis	Total	# Surv.	% Surv.
MAS	2212	2058	93
RDS	813	688	85
CDH	1091	668	61
Pneumonia/ Sepsis	805	619	77
ALS	23	14	61
PPHN	739	642	87
Others	180	142	79
Total	5863	4831	82

...continued

PEDIATRIC RESPIRATORY CASES BY YEAR

Year	Total	# Surv.	% Surv.
1982-87	26	9	35
1988	35	13	37
1989	50	26	52
1990	113	52	46
1991	85	47	55
Total	309	147	48

PEDIATRIC RESPIRATORY CASES BY DIAGNOSIS

Primary Diagnosis	Total	# Surv.	% Surv.
Bacterial pneumonia	27	12	44
Viral pneumonia	97	46	47
Intrapulmonary hemorrhage	4	4	100
Aspiration	33	20	61
Pneumocystis	6	2	33
ARDS	82	34	41
Others	60	29	48

CARDIAC SUPPORT CASES BY YEAR
(neonate and pediatric)

Year	Total	# Surv.	% Surv.
1982-87	97	53	55
1988	60	25	43
1989	109	55	50
1990	158	66	42
1991	121	50	41
Total	545	250	46

CARDIAC SUPPORT CASES BY AGE GROUP

Age	Total	# Surv.	% Surv.
Neonate	246	121	49
Pediatric	299	129	43

CARDIAC SUPPORT CASES BY DIAGNOSIS
(neonate and pediatric)

Primary Diagnosis	Total	# Surv.	% Surv.	
Cardiac surgery	480	213	44	(see surgery type below)
Cardiac transplant	20	6	30	
Myocarditis	21	17	81	
Myocardiopathy	15	6	40	
Others	9	8	89	
Total	545	250		

CARDIAC SURGERY CLASSIFICATIONS

Surgery Type	Total	# Surv.	% Surv.
LEFT TO RIGHT SHUNT (PDA, ASD, VSD, AVSD, AV canal, Endocardial Cushion Defect)	80	42	52
LEFT-SIDED OBSTRUCTIVE LESIONS (Aortic Stenosis, Mitral Stenosis, Coarctation)	17	6	35
HYPOPLASTIC LEFT HEART SYNDROME	10	4	40
RIGHT-SIDED OBSTRUCTIVE LESIONS (Pulmonary Stenosis, Pulmonary Atresia, Tricuspid Atresia)	37	13	35

...continued

Surgery Type	Total	# Surv.	% Surv.
CYANOTIC INCREASES PULMONARY FLOW (Truncus Arterious, Transposition of Great Vessels)	85	28	33
CYANOTIC INCREASED PULMONARY CONGESTION (TAPVR, PAPVR)	79	41	52
CYANOTIC DECREASED PULMONARY FLOW (Tetrology of Fallot, Double Outlet Right Ventricle, Ebstrein's Anomaly)	95	47	49
ANOMALOUS LEFT CORONARY ARTERY	11	5	45
POSTOPERATIVE LESION: FONTAN	25	5	20
MISCELLANEOUS	41	22	54
Total	480	213	

ADULT CASES BY YEAR

Year	Total	# Surv.	% Surv.
1985	1	0	0
1986	1	0	0
1987	1	1	100
1988	9	1	11
1989	4	2	50
1990	17	10	59
1991	18	5	28

Total adult cardiac = 15
Total adult pulmonary = 36

ADULT CASES BY DIAGNOSIS

Respiratory Diagnosis:	Total	# Surv.	% Surv.
Bacterial pneumonia	4	1	25
Viral pneumonia	7	6	86
Intrapulmonary hemorrhage	1	0	0
Aspiration	3	0	0
ARDS	13	8	67
Other respiratory	8	2	25
Cardiac Diagnosis:			
Pre/post transplant	7	2	29
Mitral valve replacement	2	0	0
Other cardiac	6	0	0

APPENDIX III

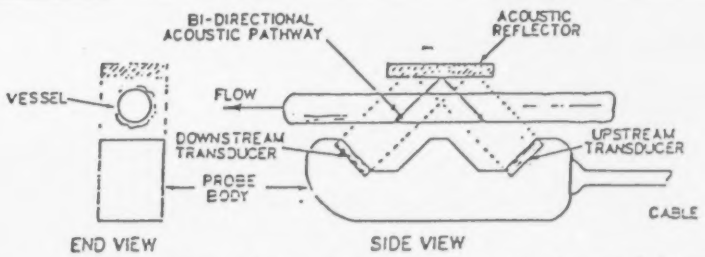
TRANSONIC FLOWMETERS-THEORY OF OPERATION

The Transonic flowprobe (Figures A-C), consists of a probe body housing two ultrasonic transduders which are positioned on one side of a vessel or tube under study and a fixed acoustic reflecter bracket situated midway between the two transducers on the opposite side of the vessel or tube. The flow meter's electronic circuitry operates the flowprobe through the following cycles:

Upstream transit-time measurement cycle: An electrical excitation causes the downstream transducer to emit a plane wave of ultrasound. This wave passes through the vessel or tubing under study in the upstream direction, bounces off the "acoustic reflector", passes again through the vessel, and is received by the upstream transducer where it is converted into electrical signals. The flowmeter analyzes and records the signals as an accurate measure of the "transit-time" it took for the wave of ultrasound to pass from one transducer to the other.

Downstream transit-time measurement cycle: The same transmit-receive sequence of the upstream cycle is repeated, but with the transmitting and receiving functions of the transducers reversed so that the liquid flow under study is bisected by an ultrasonic wave in the downstream direction. Again , the flowmeter derives and records from this transmit-receive sequence an accurate measure of the transit-time.

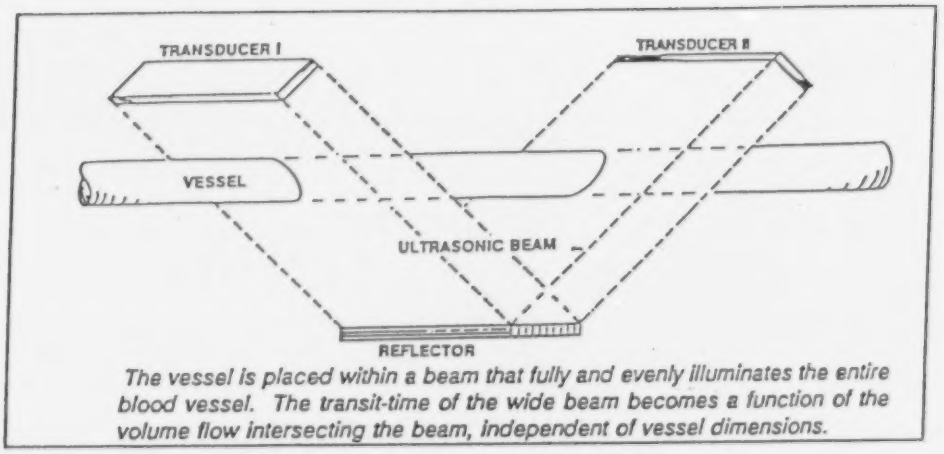
FIGURE A



Schematic views of the perivascular Transonic ultrasonic volume flowsensor. Two transducers pass ultrasonic signals back and forth, alternately crossing the flowing liquid in upstream and downstream direction. The difference in travel time of the upstream and downstream signals is a measure of volume flow.

Just as the speed of a swimmer depends in part on water currents, so is transit-time measured by the flowprobe affected by motion in the ultrasonic-conducting medium; i.e., by the flow of blood or other liquid through the vessel or tubing. On the upstream cycle, the sound wave travels against the flow which **increases the total transit-time** by a flow-dependent amount. In the **downstream** cycle, the sound wave travels with the flow which **decreases the total transit-time** by the same amount. Flowmeter circuitry then subtracts the downstream from the upstream transit-time. Through the design of the ultrasonic transducers, this difference signal is a measure of **volume flow**.

FIGURE B

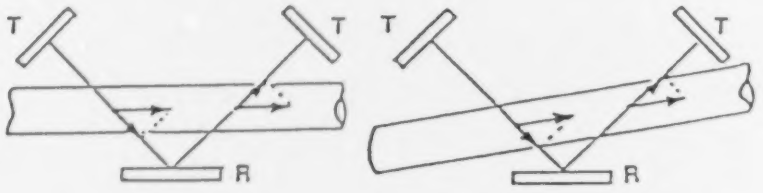


The vessel is placed within a beam that fully and evenly illuminates the entire blood vessel. The transit-time of the wide beam becomes a function of the volume flow intersecting the beam, independent of vessel dimensions.

A single ray of the ultrasonic beam "picks up" a shift in transit time proportional to average velocity, and the path length over which this velocity is encountered. Because of the side-beam ultrasonic illumination (Figure B), the receiving transducer sums (integrates) this velocity-vessel chord product over the full width of the vessel, and yields average velocity times vessel inside area. Rays of the beam which cross the acoustic window without intersecting the vessel give a zero-contribution to the volume flow integral. Therefore, volume flow in sensed even when the vessel is much smaller than the vessel window and independent of the velocity profile of the flow.

(Taken from Transonic Flowmeters Operator's Manual 1990, pp. 5-6.)

FIGURE C



Angle Insensitivity of Transonic flowprobe: (T) = transducer; (R), reflector

a) The ultrasonic beam intersects the vessel twice on its reflective pathway. During each intersection, the transit-time of the beam is modified by a vector component of the flow. The full transit-time of the ultrasonic beam senses the sum of these two vector components, that is, the flow itself.

b) With misalignment, one vector component of the flow becomes greater and the second vector component diminishes, with little consequence to their sum.

Furthermore, as a result of the ultrasonic wave's reflective pathway, the Transonic flowprobe senses the forward axial component of flow and is largely insensitive to vessel/probe misalignment (Figure C).

FIGURE 1

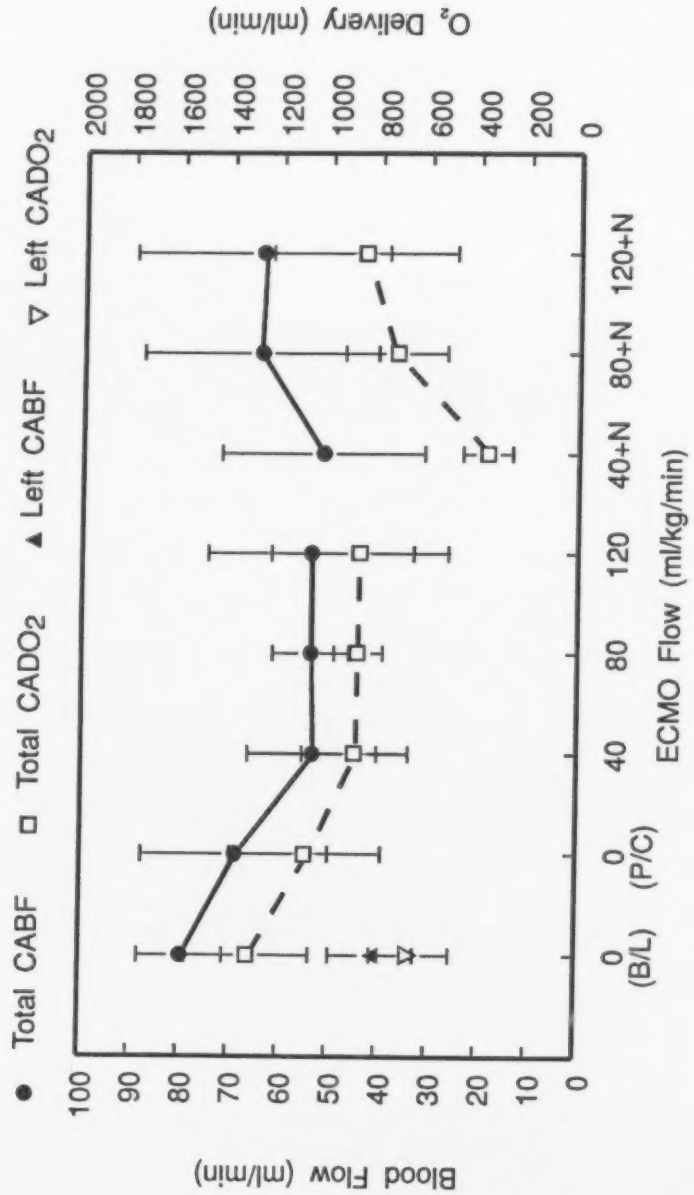

● Total CABF
□ Total CADO2
▲ Left CABF
▽ Left CADO2
Blood Flow (ml/min)
O2 Delivery (ml/min)
100
90
80
70
60
50
40
30
20
10
0
2000
1800
1600
1400
1200
1000
800
600
400
200
0
0 (B/L)
0 (P/C)
40
80
120
40+N
80+N
120+N
ECMO Flow (ml/kg/min)

FIGURE 2

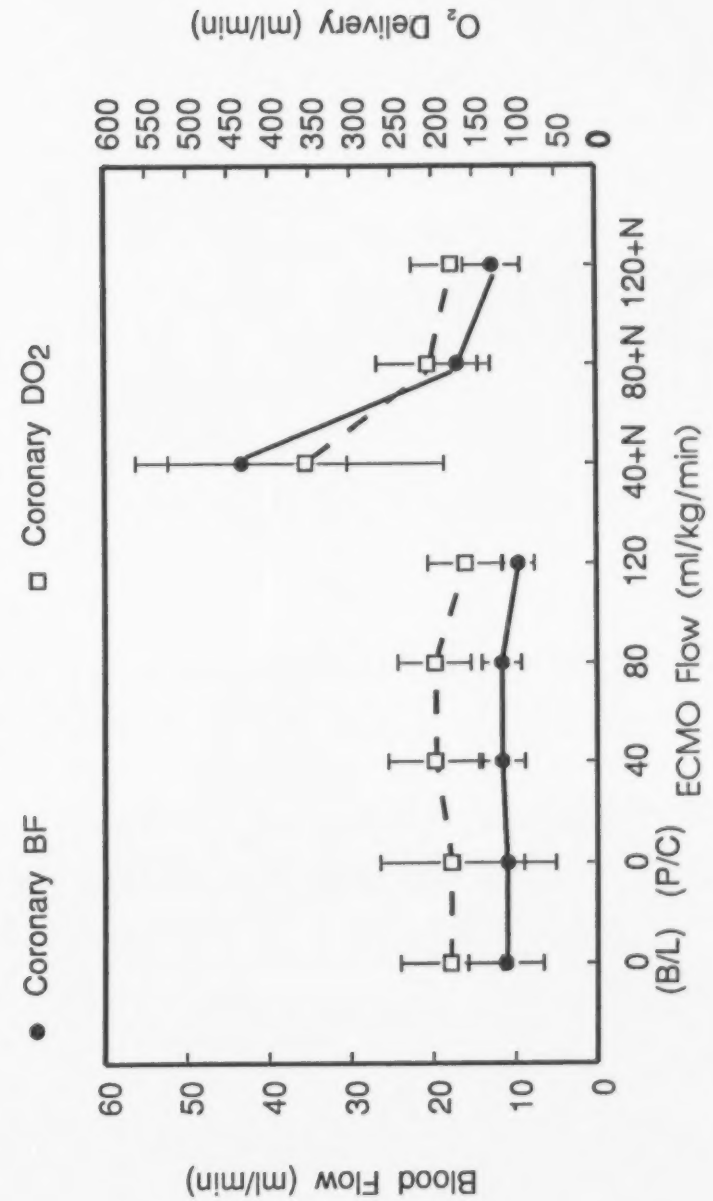

O2 Delivery (ml/min)
600
550
500
450
400
350
300
250
200
150
100
50
0
Blood Flow (ml/min)
60
50
40
30
20
10
0
● Coronary BF
□ Coronary DO2
0 (B/L)
0 (P/C)
40
80
120
40+N
80+N
120+N
ECMO Flow (ml/kg/min)

FIGURE 3

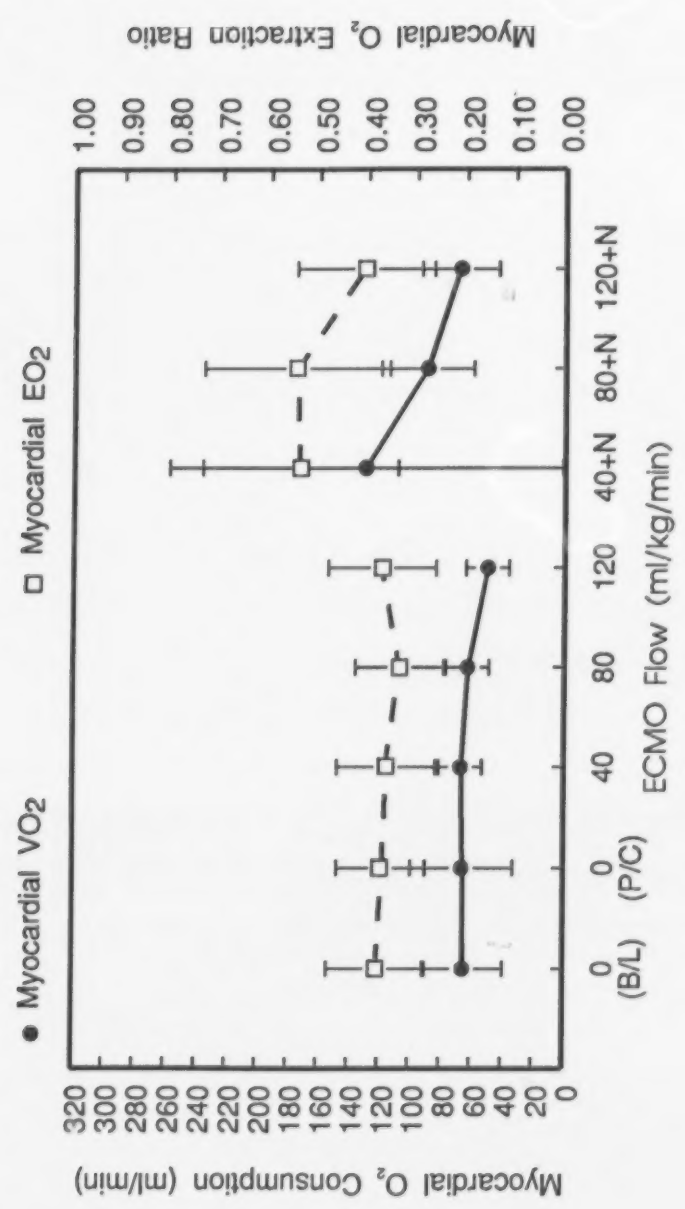

Myocardial O2 Extraction Ratio
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
Myocardial O2 Consumption (ml/min)
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
● Myocardial VO2
□ Myocardial EO2
0 (B/L)
0 (P/C)
40
80
120
40+N
80+N
120+N
ECMO Flow (ml/kg/min)

FIGURE 4

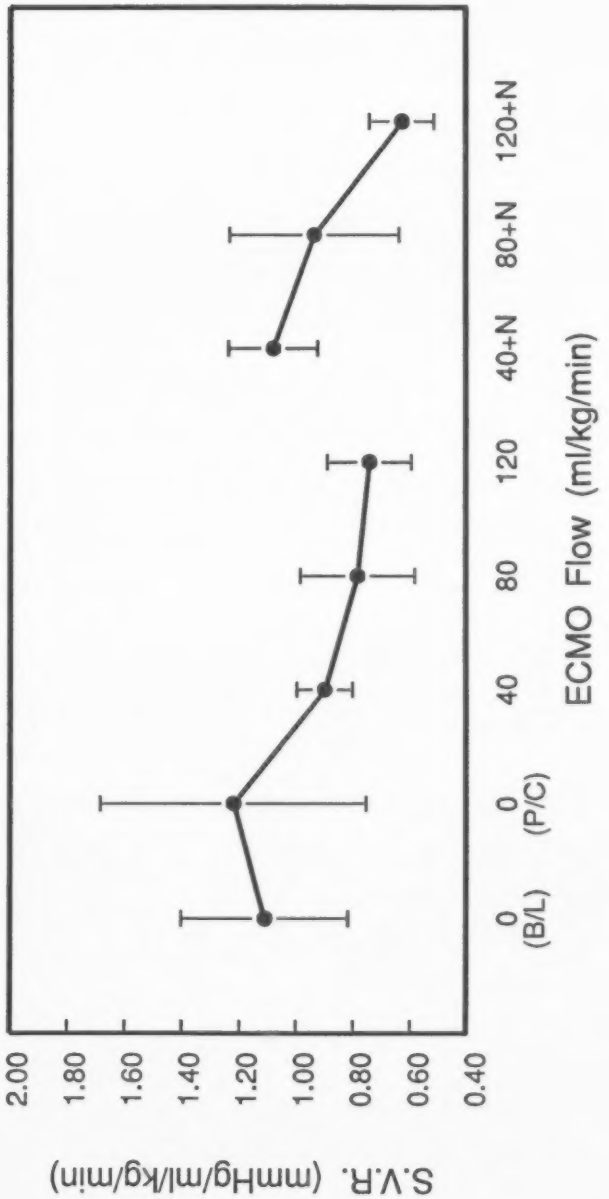

S.V.R. (mmHg/ml/kg/min)
2.00
1.80
1.60
1.40
1.20
1.00
0.80
0.60
0.40
0 (B/L)
0 (P/C)
40
80
120
40+N
80+N
120+N
ECMO Flow (ml/kg/min)

FIGURE 5

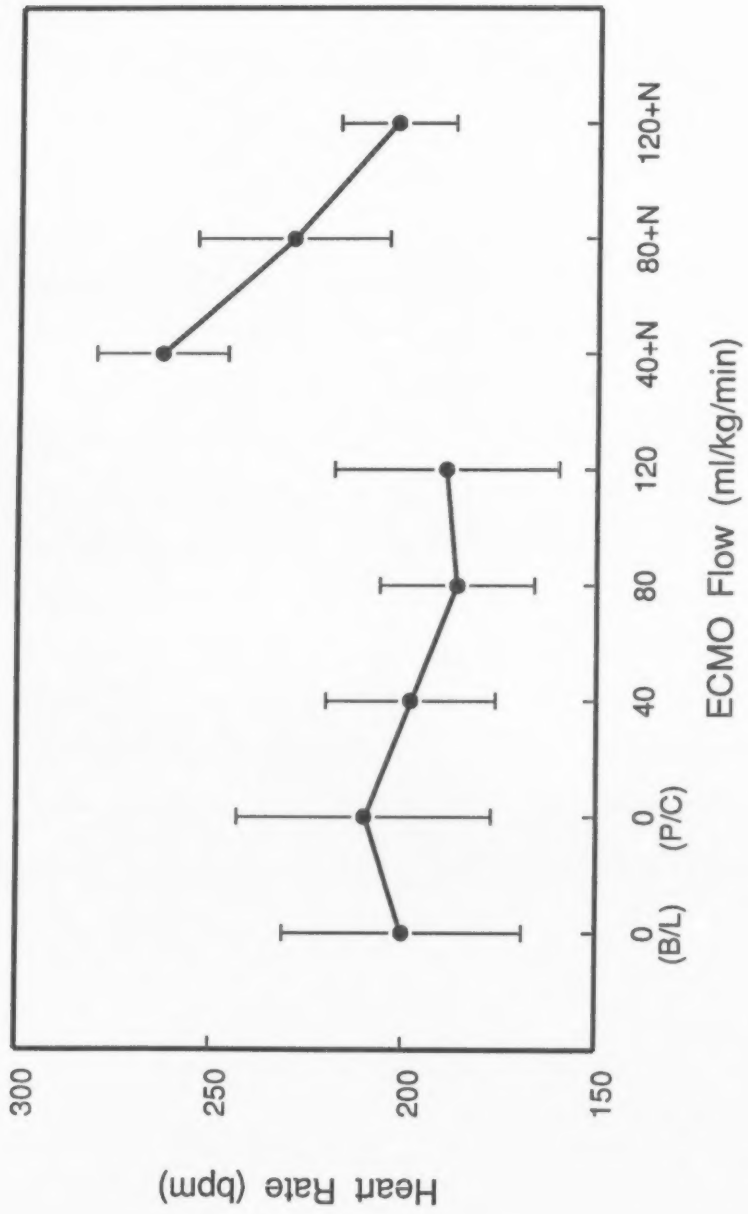

Heart Rate (bpm)
300
250
200
150
0 (B/L)
0 (P/C)
40
80
120
40+N
80+N
120+N
ECMO Flow (ml/kg/min)

FIGURE 6

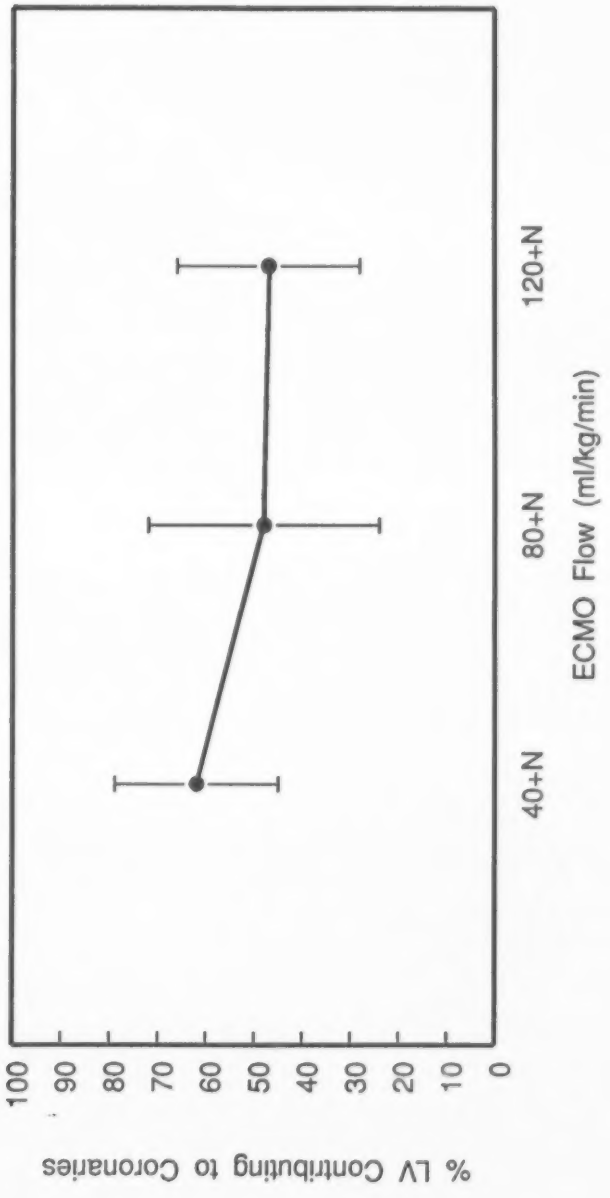

% LV Contributing to Coronaries
100
90
80
70
60
50
40
30
20
10
0
40+N
80+N
120+N
ECMO Flow (ml/kg/min)

FIGURE 7

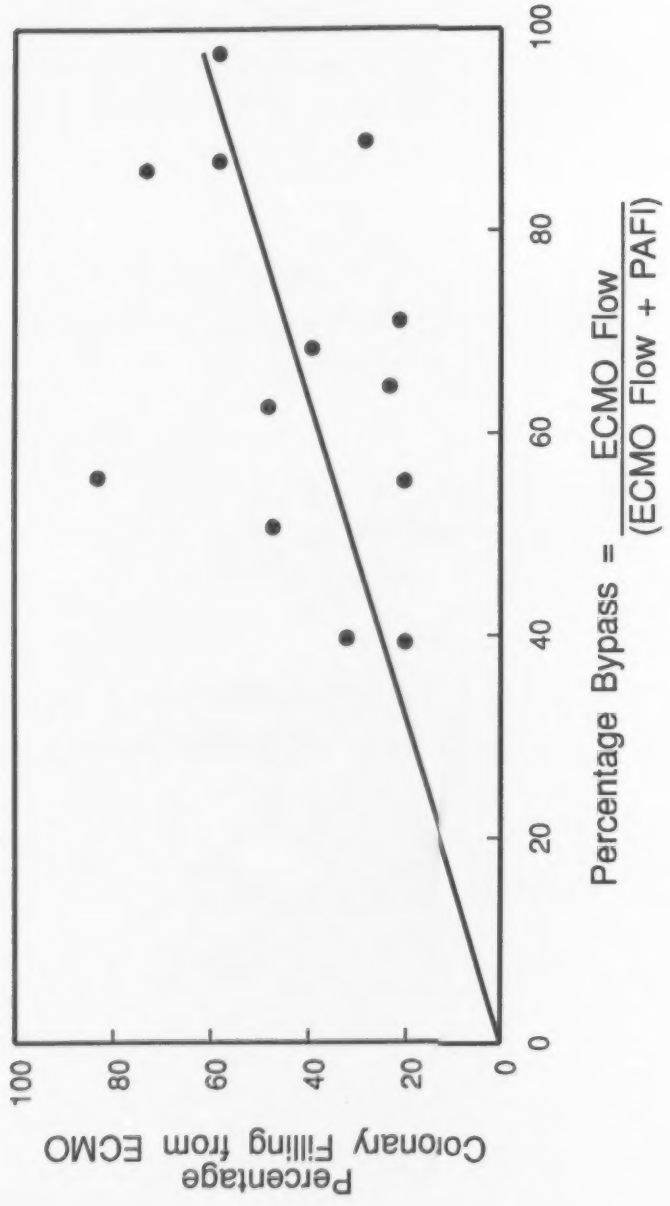

Percentage Coronary Filling from ECMO
100
80
60
40
20
0
0
20
40
60
80
100
Percentage Bypass = ECMO Flow / (ECMO Flow + PAFI)

FIGURE 8

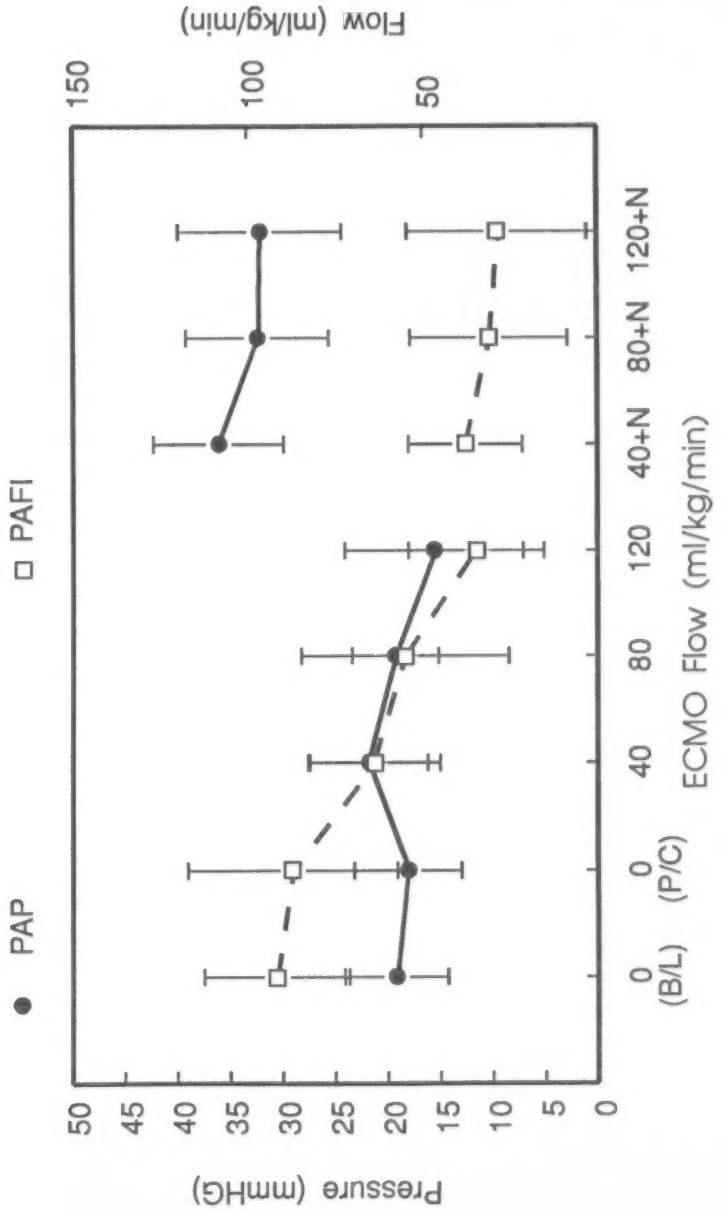

Flow (ml/kg/min)
150
100
50
Pressure (mmHG)
50
45
40
35
30
25
20
15
10
5
0
● PAP
□ PAFI
0 (B/L)
0 (P/C)
40
80
120
40+N
80+N
120+N
ECMO Flow (ml/kg/min)

FIGURE 9

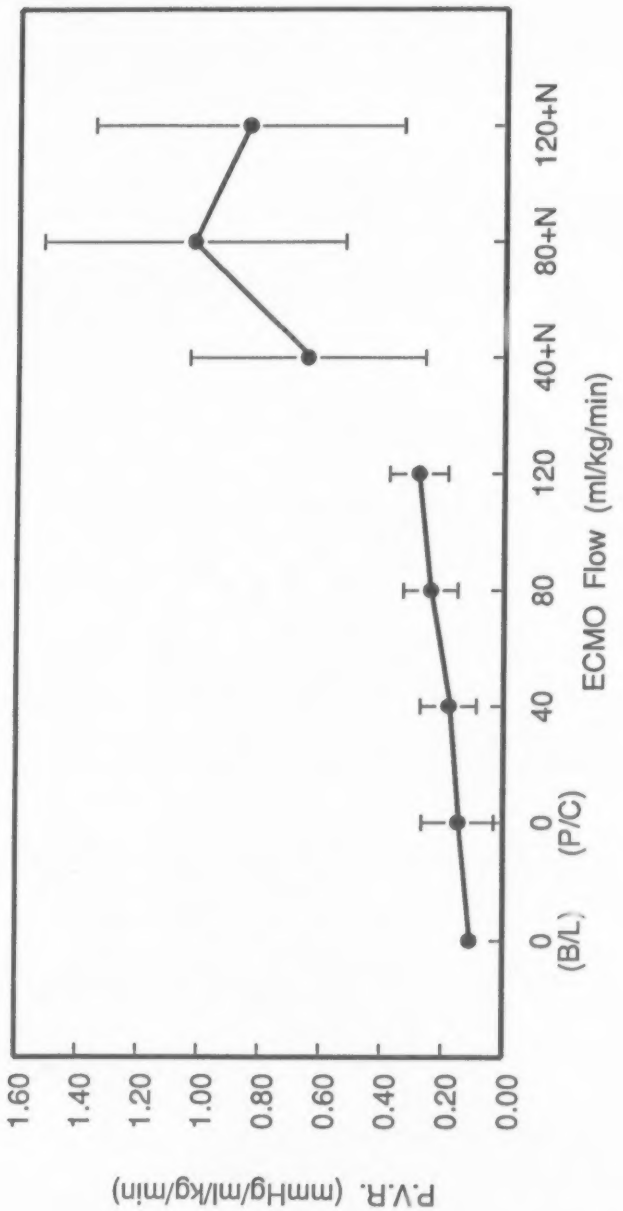

P.V.R. (mmHg/ml/kg/min)
1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
0 (B/L)
0 (P/C)
40
80
120
40+N
80+N
120+N
ECMO Flow (ml/kg/min)

FIGURE 10

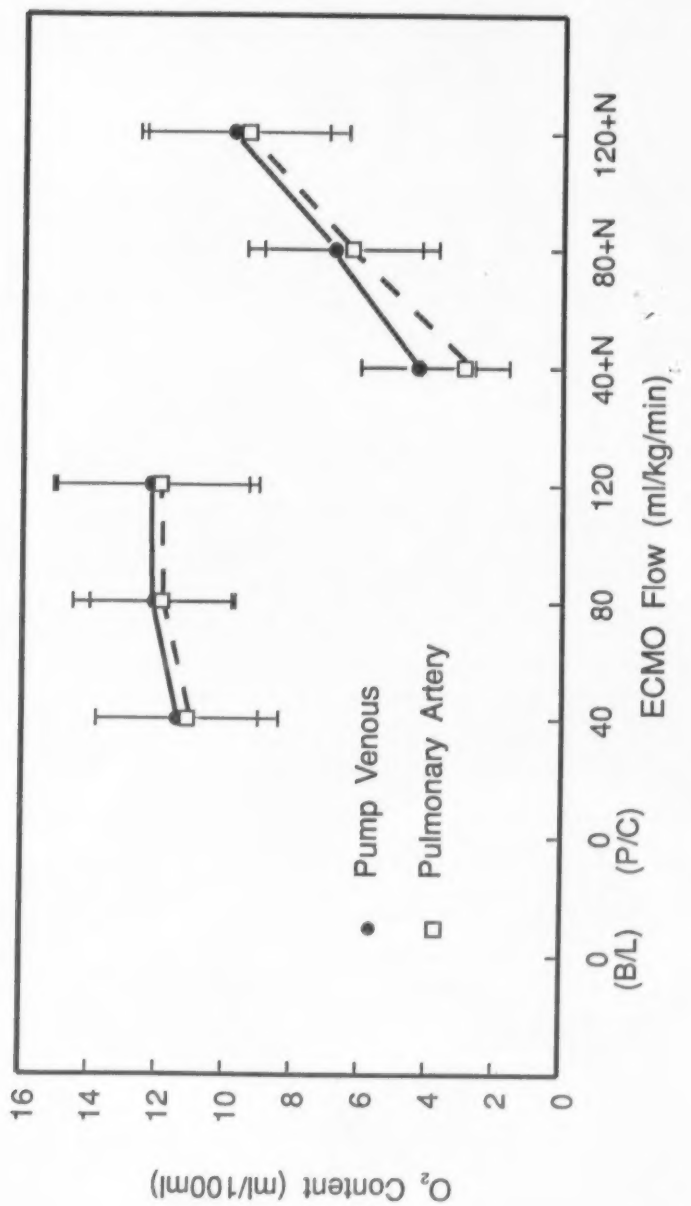

O2 Content (ml/100ml)
16
14
12
10
8
6
4
2
0
Pump Venous
Pulmonary Artery
0 (B/L)
0 (P/C)
40
80
120
40+N
80+N
120+N
ECMO Flow (ml/kg/min)

FIGURE 11

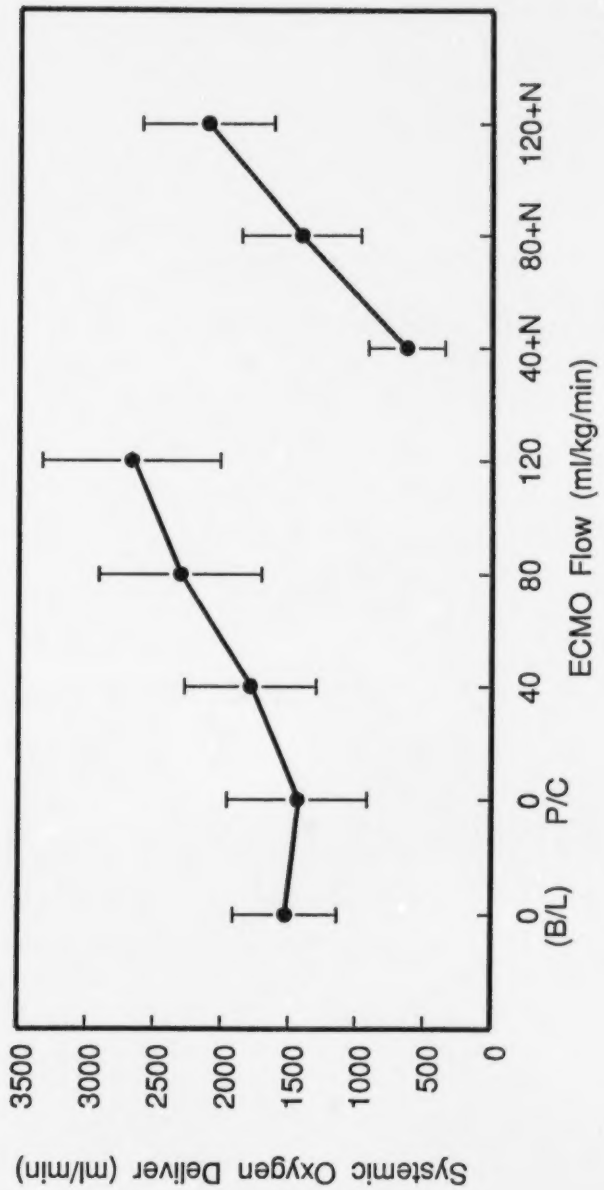

Systemic Oxygen Deliver (ml/min)
3500
3000
2500
2000
1500
1000
500
0
0 (B/L)
0 P/C
40
80
120
40+N
80+N
120+N
ECMO Flow (ml/kg/min)

FIGURE 12

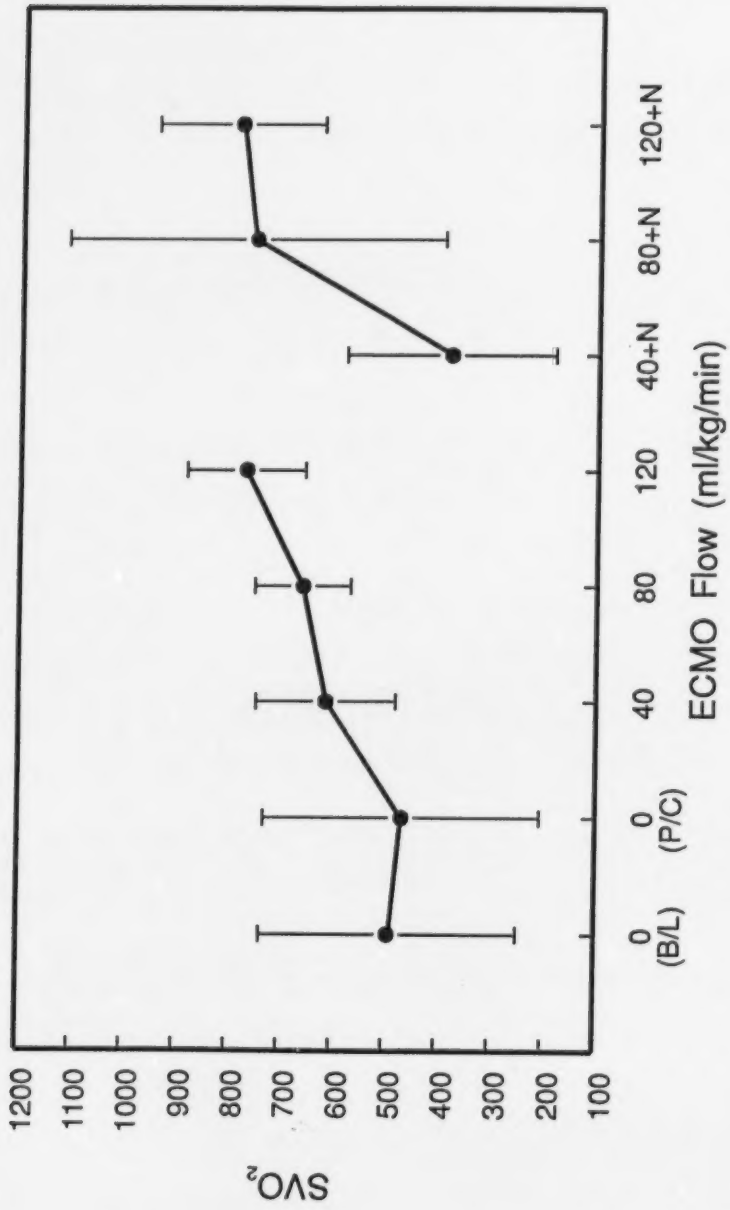
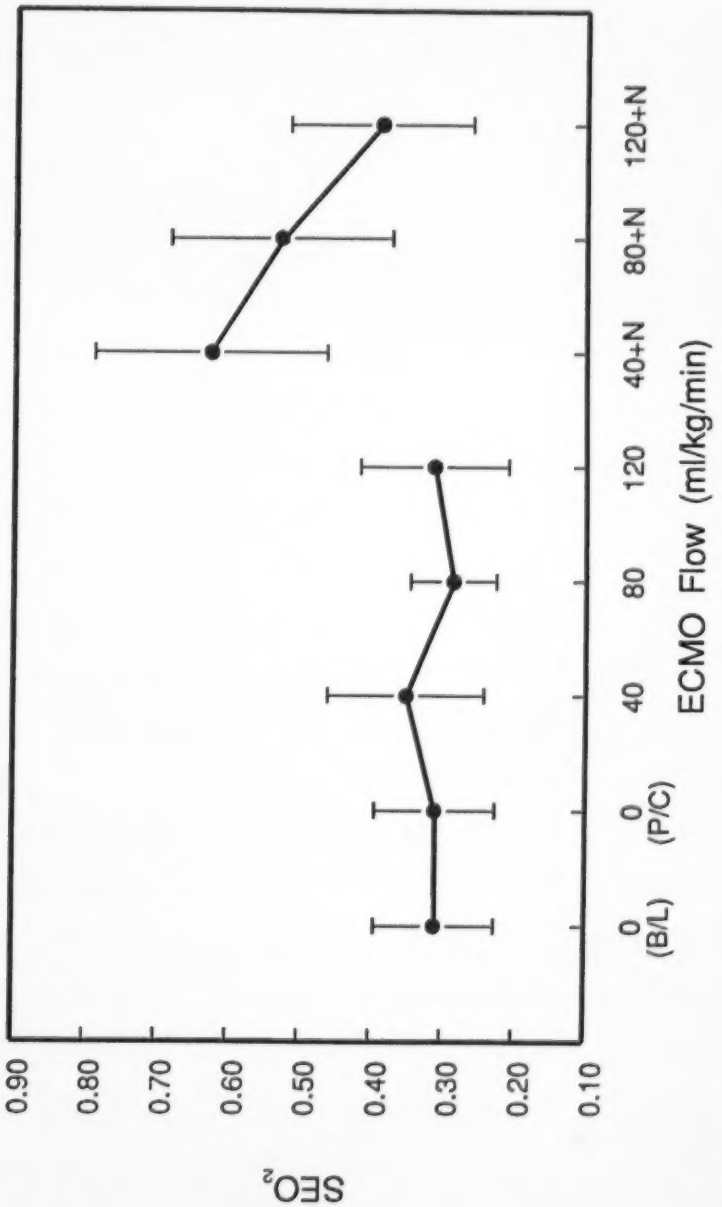

SVO2
1200
1100
1000
900
800
700
600
500
400
300
200
100
0 (B/L)
0 (P/C)
40
80
120
40+N
80+N
120+N
ECMO Flow (ml/kg/min)

FIGURE 13


SEO2
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0 (B/L)
0 (P/C)
40
80
120
40+N
80+N
120+N
ECMO Flow (ml/kg/min)